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4

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Authors should supply their qualifications, main appointment, and the name and address of the hospital or the laboratory.

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The text of articles submitted for publication should be typewritten in double-spacing on paper sheet size 22 × 32 cm (A4). There should be a minimum margin of 3 cm all round. The pages should be numbered.

Reports on clinical or laboratory investigation should as far as possible be organised into the following main sections: (1) Introduction, (2) Objective(s), (3) Patients or Materials, (4) Procedures or Methods, (5) Findings or Results, (6) Discussion and (7) Conclusions with (8) a Summary at the end.

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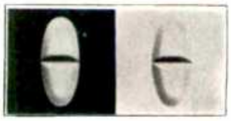

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Studies in depth

Amoxil compared with ampicillin

When Amoxil was first introduced to the Medical Profession in May 1972 it was hailed as the successor to ampicillin. Since then research teams and clinical trial workers all over the world have reported that Amoxil is superior to ampicillin. Some of their reports have been in areas which were anticipated, but others have confirmed important superiorities which could not be predicted. These reports are obviously of considerable interest to the discerning clinician, and inevitably there have been many requests for a compendium of the available work. This is now available and will be sent upon request to interested clinicians. Brief summaries of the main areas considered in the compendium are given below.

More effective than ampicillin

There is evidence that Amoxil is more effective than ampicillin and this is particularly well illustrated in respiratory infections. Indeed, some reports have confirmed that Amoxil can succeed where ampicillin has failed[1,2,3]

Absorption unaffected by food

Early reports confirmed that Amoxil is twice as well absorbed as ampicillin, giving a peak serum concentration of 5.3 µg/ml[4] as opposed to ampicillin's 2.3 µg/ml[5]. Further work has shown that if both drugs are taken in the non-fasting state the overall absorption of Amoxil over the following 6 hour period is not significantly reduced, whereas that of ampicillin is reduced by nearly a third.

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Studies at the Brompton Hospital[6] have shown that whereas ampicillin penetrates well into purulent sputum it penetrates very poorly into mucoid sputum. These workers have shown that Amoxil penetrates equally well into both purulent and mucoid sputum, and suggest that this may have far-reaching consequences in the treatment of respiratory infections.

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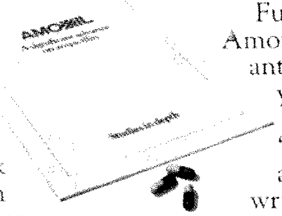

AMOXIL

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References: (1) Brit. J. Dis. Chest., (1972), 66, 185. (2) S.A. med. J., (1973), 47, 717. (3) Chemotherapy, (1973), 18, (Suppl.), 19. (4) Brit. med. J., (1972), 3, 13. (5) Antimicrobial Agents and Chemotherapy (1970), 438. (6) To be published (7) Antimicrobial Agents and Chemotherapy, (1970), 416.

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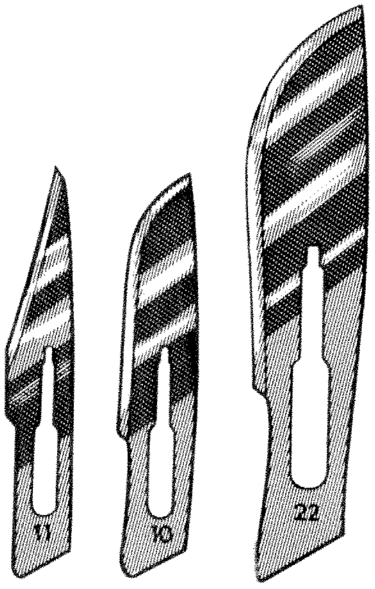

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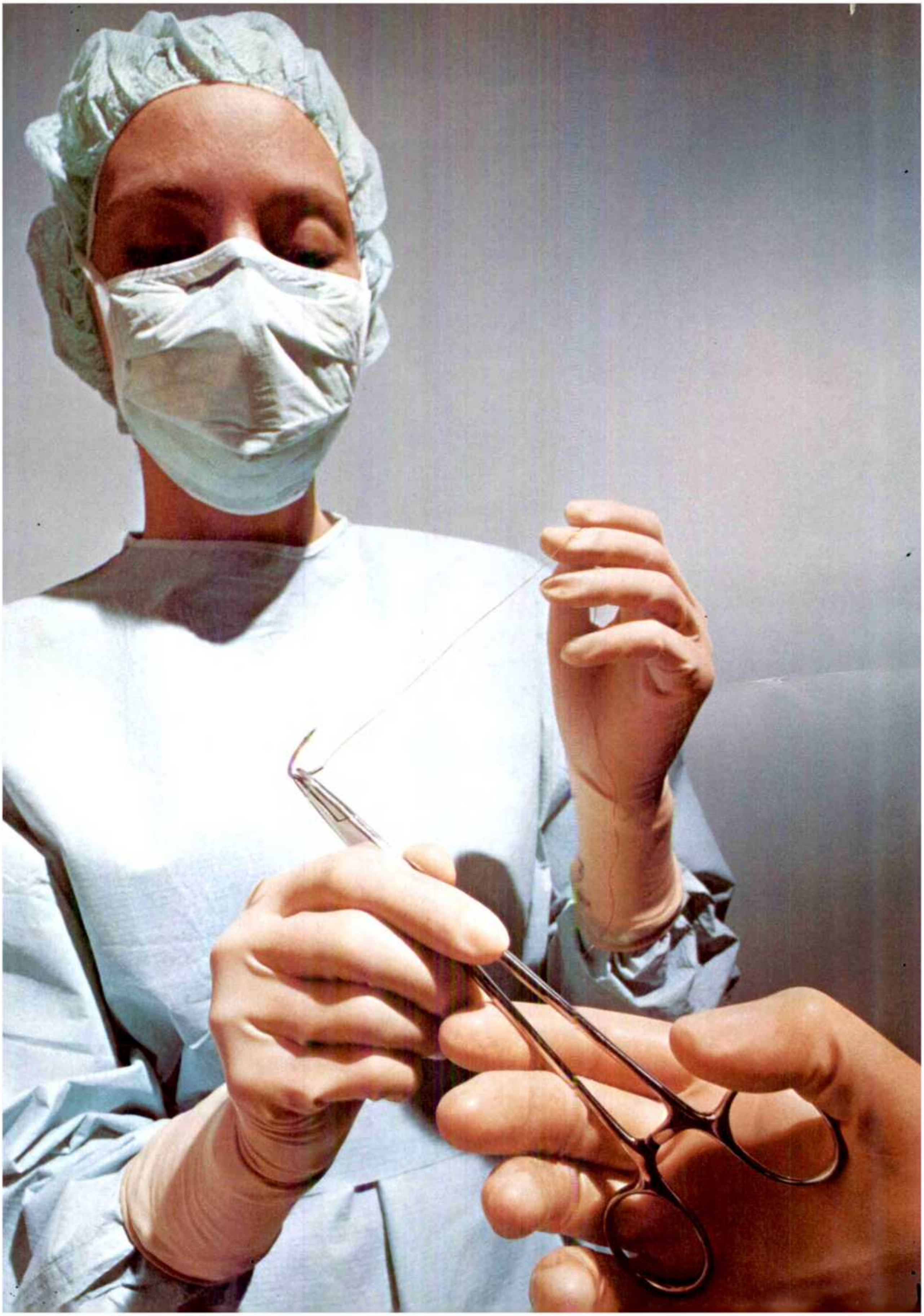

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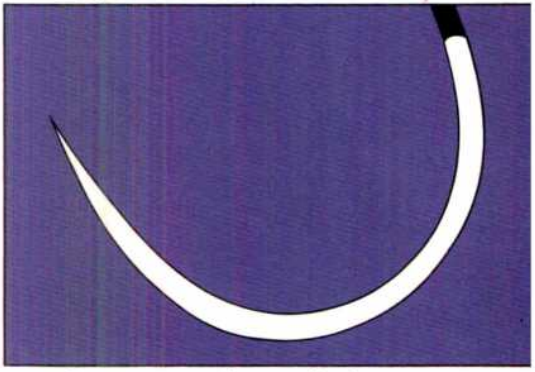

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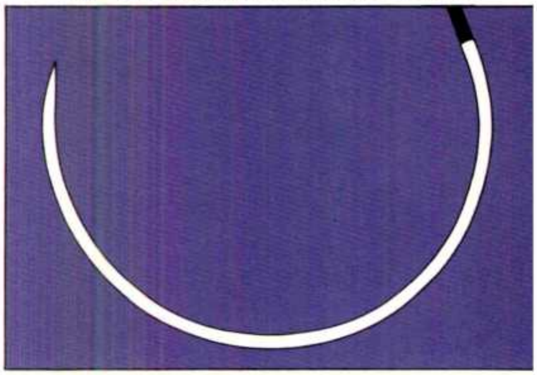

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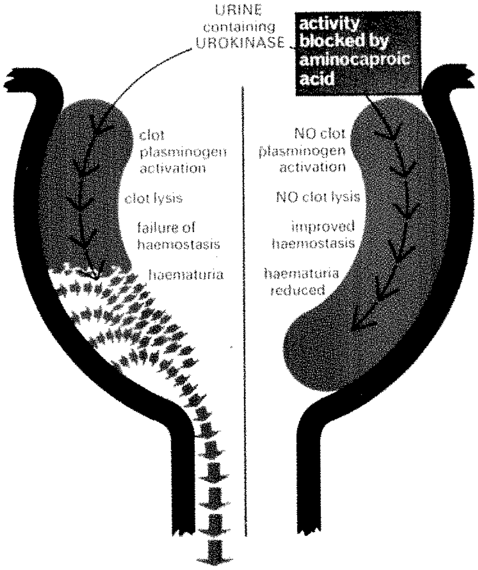

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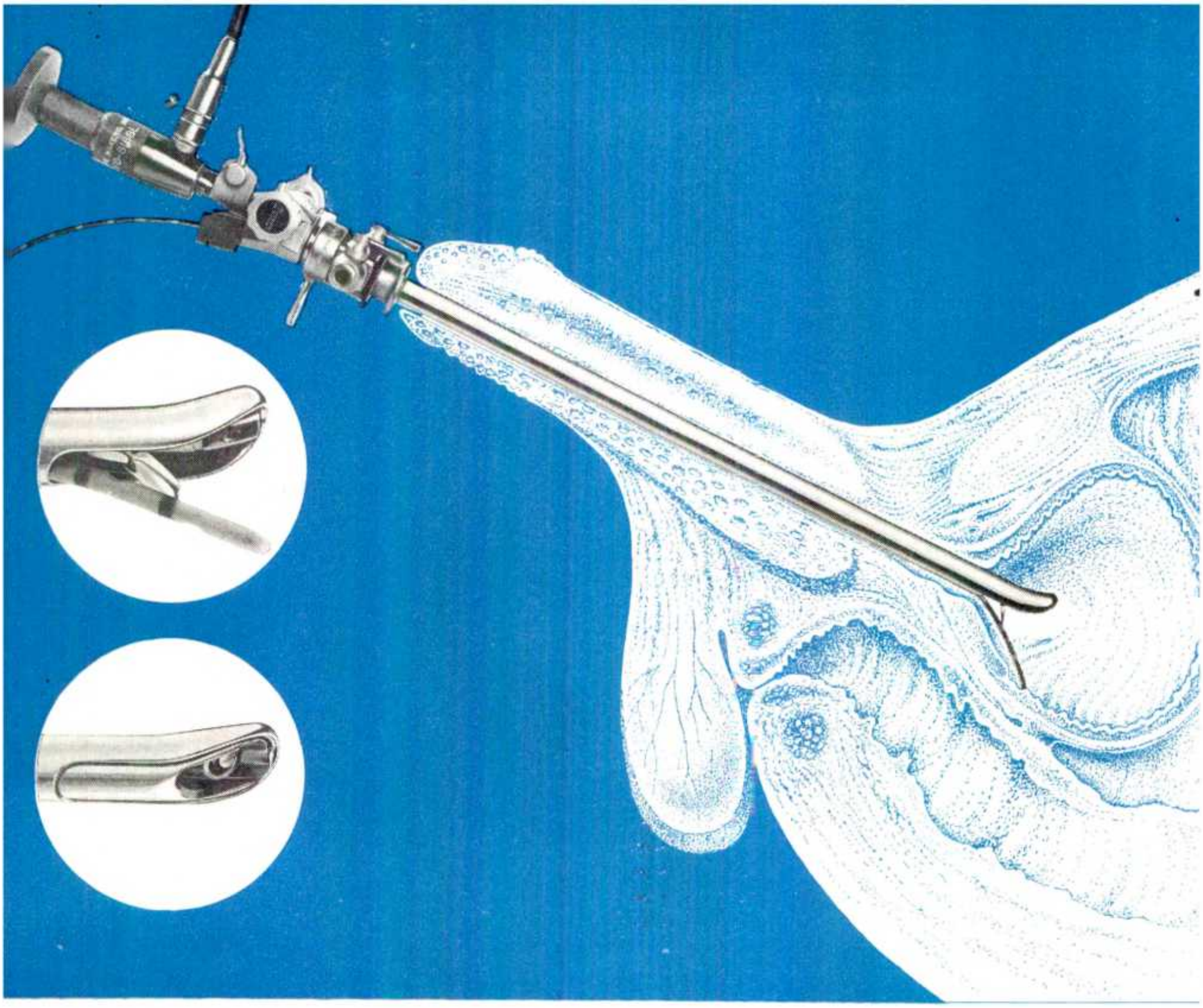

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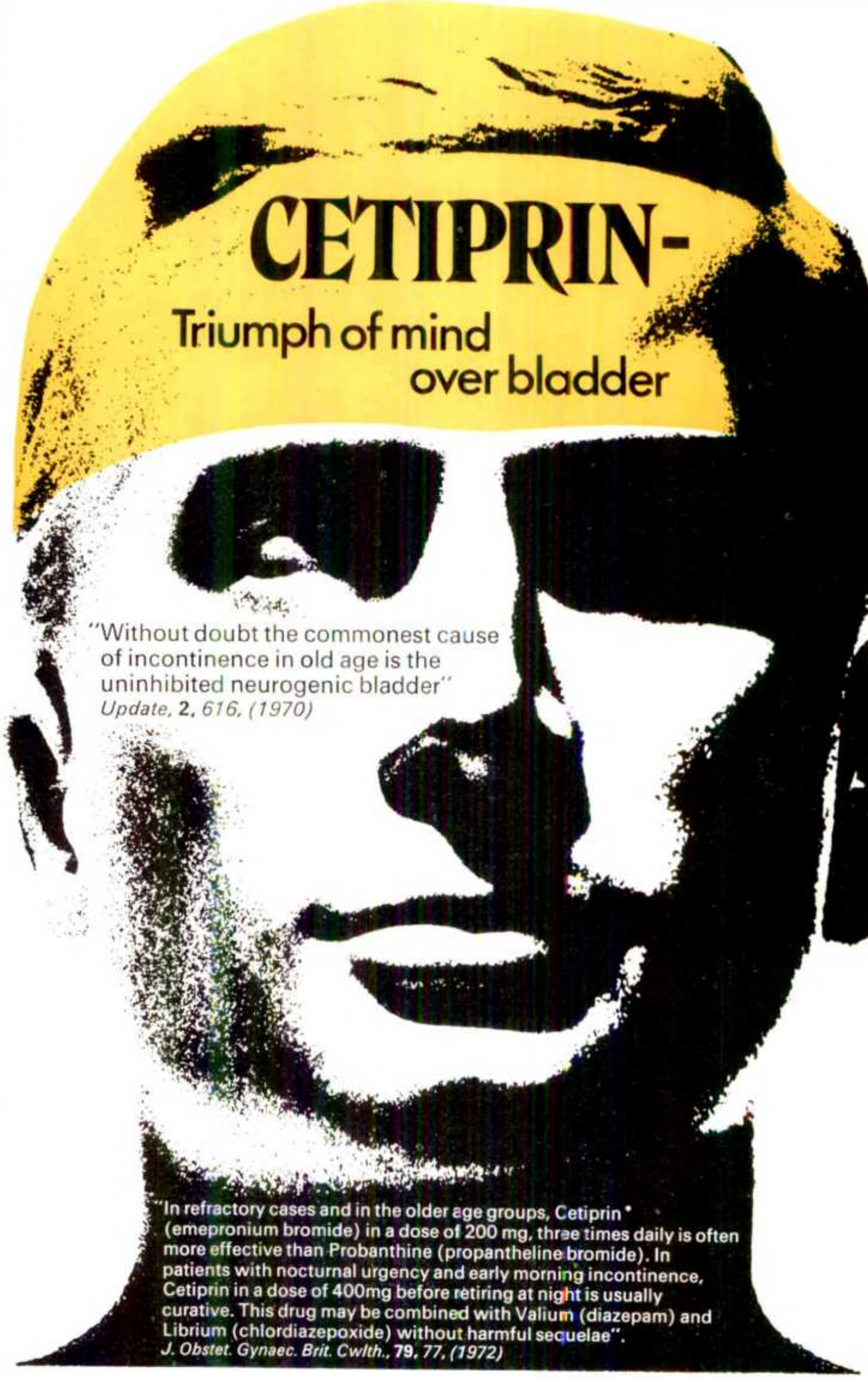

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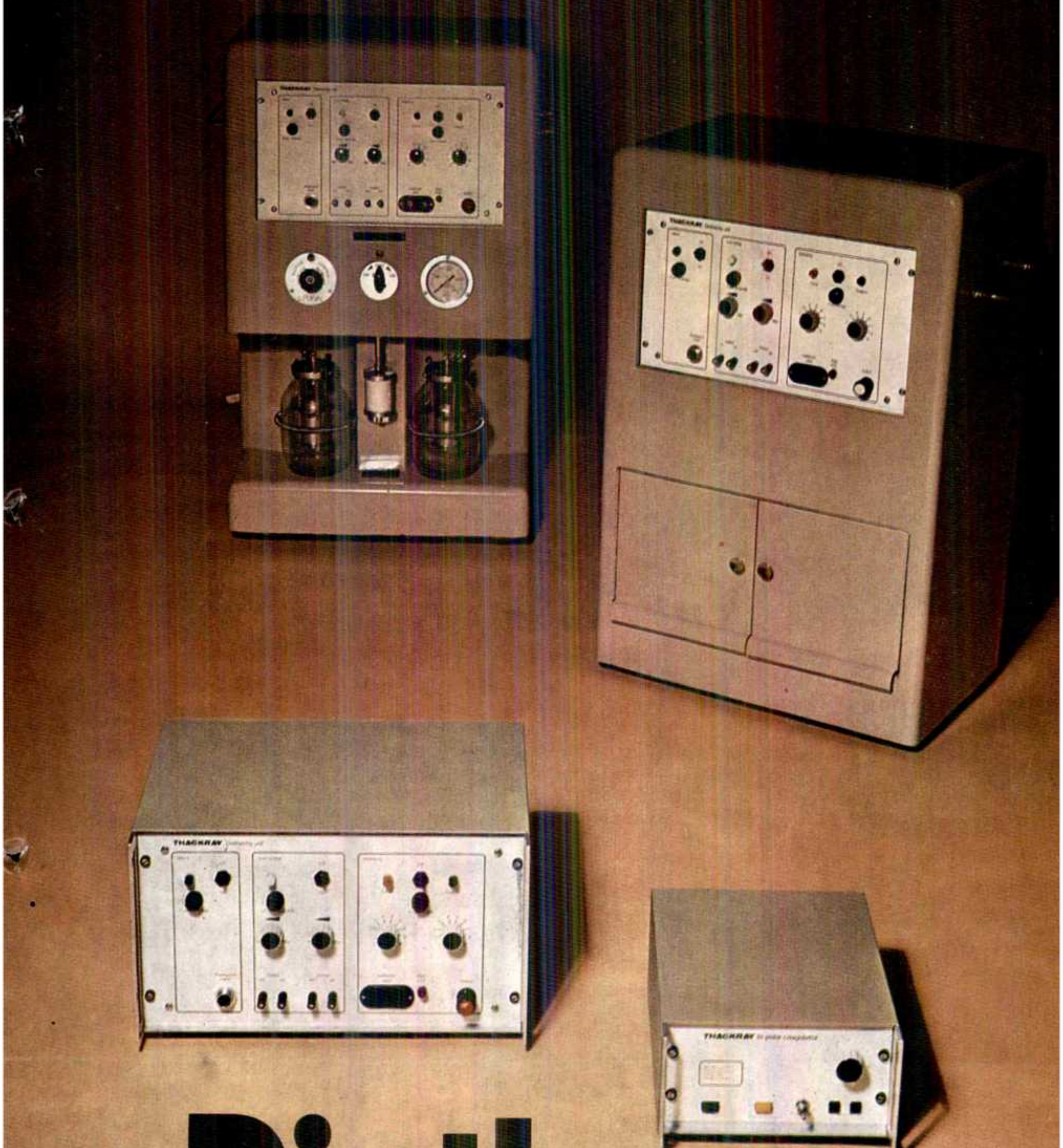

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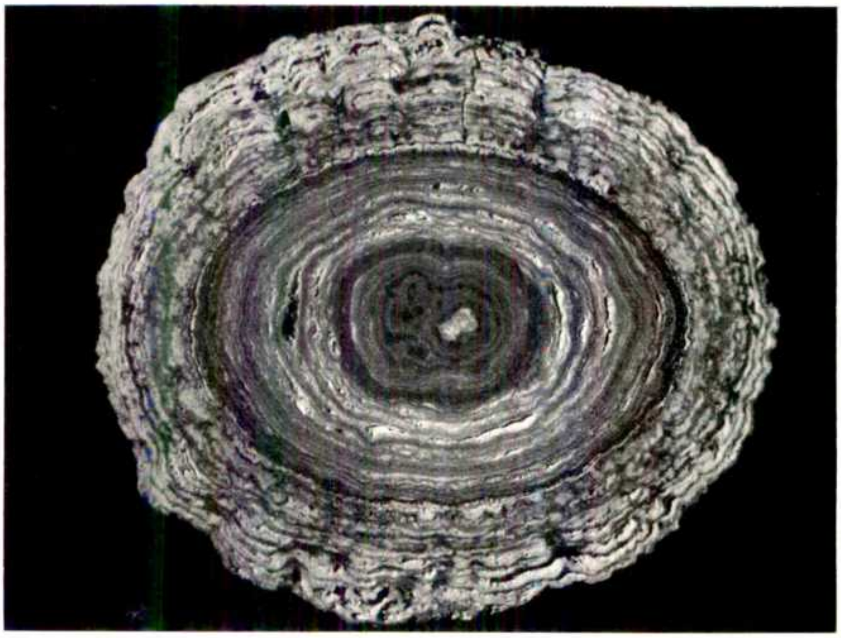

Proceedings of the International Symposium on Renal Stone Research, Madrid, September 1972
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T.N.M. Classification for Urological Tumours (U.I.C.C.)—1974

D. M. WALLACE, G. D. CHISHOLM and W. F. HENDRY

Institute of Urology, London

The aim of any descriptive classification of tumours is to be both retrospective and prospective, to allow an analysis of past clinical material (provided that this material has been adequately documented), and to be of use in future planning of various modalities of therapy. A classification must be sufficiently simple to enable it to be used by the majority of clinicians, yet able to incorporate special features for subsequent analysis without adding to the complexity. It must be simple—but it must be precise—and the terms must be used accurately. The terms must have the significance of "appellation contrôlée". This term, as applied to French wines, is a guarantee that the label on the bottle is a true description of the contents—nothing has been added and nothing has been taken away. The T.N.M. symbols must be used in the same way, to mean exactly what has been defined—no more—no less.

To Stage or to Classify?

When one uses a staging system—Stage 1, Stage 2, etc.—a variety of factors are incorporated into one group and it becomes impossible to separate out from such a group those factors which are important, either for selection of treatment or in prognosis.

The Tumour Node Metastasis classification is a shorthand method, but essentially a descriptive method for recording a variety of factors which may be of importance in therapy or prognosis. Originally described in 1952 by Denoix, this system has been applied to many sites within the body, based on general principles, and is now widely used internationally.

The most important point of the T.N.M. classification is that it is applicable to all patients fit for clinical and radiological examination. The Dukes-Masina and the Jewett-Strong-Marshall staging systems were designed originally for the description of operative specimens but, when the same descriptive terms were used for clinical observations, confusion arose between the clinical and the pathological groups. The object of the T.N.M. classification is to make a sharp distinction between a series of patients treated on the basis of a clinical assessment which has an intrinsic error of staging, and a series of cases treated by excisional surgery, which is very much more accurate but obviously is a more limited form of classification. It is therefore important that the difference between the T (clinical assessment) and the P (pathological assessment) should be quite clearly understood.

The T.N.M. Committee of the International Union against Cancer (U.I.C.C.) convened a subcommittee which met in Rotterdam in February 1973. Their recommendations were considered by a small group of the International Society of Urology in Amsterdam in July of the same year and by several national groups since then. The U.I.C.C. committee has since discussed all proposals, and made firm recommendations which conform to the international usage of the T.N.M. system at all sites. These recommendations are reproduced in full in the appendix, and will be reviewed again in 5 years' time.

Basically, the 3 main symbols of the T.N.M. system describe:

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

T. the local extent of the primary tumour as determined by clinical and biopsy examination,
N. the clinical evidence of spread to the regional lymphatic nodes,
M. the presence of distant metastases including distant lymphatic nodes.

The Primary Tumour

Since many of the conventions are common to all sites, including non-urological sites, one can discuss firstly the general conventions and then the detailed use of the symbols in the 4 main urological sites—bladder, kidney, prostate and testes. Minimum requirements for meaningful categorisation of the tumours are defined, and these vary for each primary site. For example, clinical examination, urography, cystoscopy, bimanual examination under full anaesthesia and biopsy or transurethral section of the tumour (if indicated) are mandatory for bladder tumours. Since the kidney is largely inaccessible to clinical examination, arteriography is now required to classify kidney tumours. For testicular tumours, the information derived from orchidectomy is used to categorise the primary tumour. If these minimum requirements to assess fully the extent of the primary tumours cannot be met, the symbol TX should be used.

The symbol T0 is used when the tumour is no longer present but when there has been histological proof of a previous tumour. This symbol can be combined with N or M if the primary tumour has been treated satisfactorily but where the patient presents with evidence of nodal or metastatic spread.

The local spread of the primary tumour whether superficial or deep, whether spreading outside the organ of origin or involving adjacent organs, is designated by the symbols T1, T2, T3, T4. For all urological sites there are 4 degrees of T, each being defined on the basis either of size or extent of infiltration or a combination of the two. Each group should be ideally of approximately the same size, with comparable numbers of patients in each group, and with a significant difference in prognosis between each group.

The T.N.M. classification is applied to all patients when first seen and before any definitive treatment has been carried out.

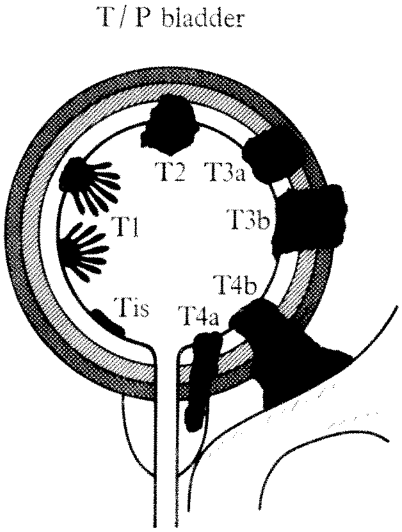


Fig. 1. T/P classification for bladder. TiS is confined to flat *in situ* carcinoma; T1 includes papillary tumours, both infiltrating and non-infiltrating, where tumour does not extend beyond lamina propria; T2—invasion of superficial muscle; T3a—invasion of deep muscle; T3b—infiltration of perivesical fat, mobile; T4a—involvement of adjoining organs; T4b—fixed (see Appendix for details).

Bladder: T—the primary tumour (Fig. 1). *T.i.S.* There has been considerable difficulty with the previous classification in differentiating between flat *in-situ* carcinoma, where there is definite marked anaplasia of surface epithelium, and papillary non-invasive carcinoma, which has a much better prognosis. Furthermore, it may sometimes be difficult to recognise a break in the basement membrane in multiple fragments of papillary carcinoma, and invaginations of surface epithelium into the subjacent lamina propria may occur in benign conditions—*e.g.* von Brunn's nests. For these reasons, the U.I.C.C. committee recommended that the category T.i.S. should be confined to true carcinoma *in situ*, which is defined as "definite anaplasia of surface epithelium without the formation of papillary structures and without infiltration" (W.H.O., 1973).

T1. This category now includes all papillary tumours, both infiltrating and non-infiltrating, where the tumour does not extend beyond the lamina propria. On bimanual examination a freely mobile mass may be felt, but this is soft, and after resection the mass is no longer palpable.

T2. The second group, where there is invasion into the superficial muscle is possibly the most difficult group to assess. Cystoscopically, one may suspect infiltration; on bimanual examination, there may be a rubbery thickening of the bladder wall but there should be no residual induration after complete transurethral resection of the lesion. In practice, this classification is usually based on a deep biopsy which shows invasion of the muscle layers. Since the depth of the biopsy cut may vary and since the thickness of the bladder wall is also variable it may be difficult to obtain an accurate distinction between superficial and deep muscle infiltration. In several series when a comparison has been made, this group has been found to be the most difficult to assess correctly. In an attempt to resolve this problem, the definition for T2 tumours has been expanded to emphasise that no residual induration should persist after transurethral resection of the lesion. If resection is not attempted, the biopsy must show invasion of only superficial muscle, and/or the bimanual examination should reveal no more than localised induration of the bladder wall.

T3. The third group is defined as when the tumour is a hard or nodular mobile mass on bimanual examination, or where the biopsy shows deep infiltration into the muscle of the bladder wall.

It has been suggested that treatment and prognosis may depend on the size of the primary tumour and that there should be a method of distinguishing between the large and small tumours. It is proposed that the group T3 be subdivided into T3a—microscopic invasion of deep muscle only, and T3b—a tumour which extends through the bladder wall.

T4. In the fourth group, the growth is fixed to the pelvic wall or involves adjoining organs by infiltration. The group where the tumour is fixed to the pelvic wall is perhaps a difficult one; it is not represented in the Jewett classification since this group is technically completely inoperable. The fixation may be due to tumour or it may be due to previous surgery or to irradiation. There is therefore intrinsically a source of error in any tumour classified as T4 since the fixation may be the result of previous inflammatory changes.

It is agreed that T4 tumours be subdivided by the addition of suffixes.

T4a Tumour invading prostate, uterus or vagina.
T4b Tumour fixed to pelvic wall and/or infiltrating the abdominal wall.

Some tumours, especially the multifocal type, tend to involve the prostate by an *in situ* change of the prostatic ducts and acini. These tumours are usually associated with non-invasive tumours elsewhere in the urinary tract, are essentially non-invasive and should be included in the T.i.S. group unless associated with an infiltrating lesion elsewhere.

Lesions of the bladder are frequently multifocal—in space by involvement of many areas of the bladder or by tumours of extravesical sites, ureter, urethra or diverticulum, or in time where tumours have appeared at multiple differing sites over a period of years. Where the disease appears to be multifocal either by simultaneous presentation of many tumours at different sites or by an asynchronous tumour formation at widely separate sites, a suffix (m) can be added to the clinical assessment.

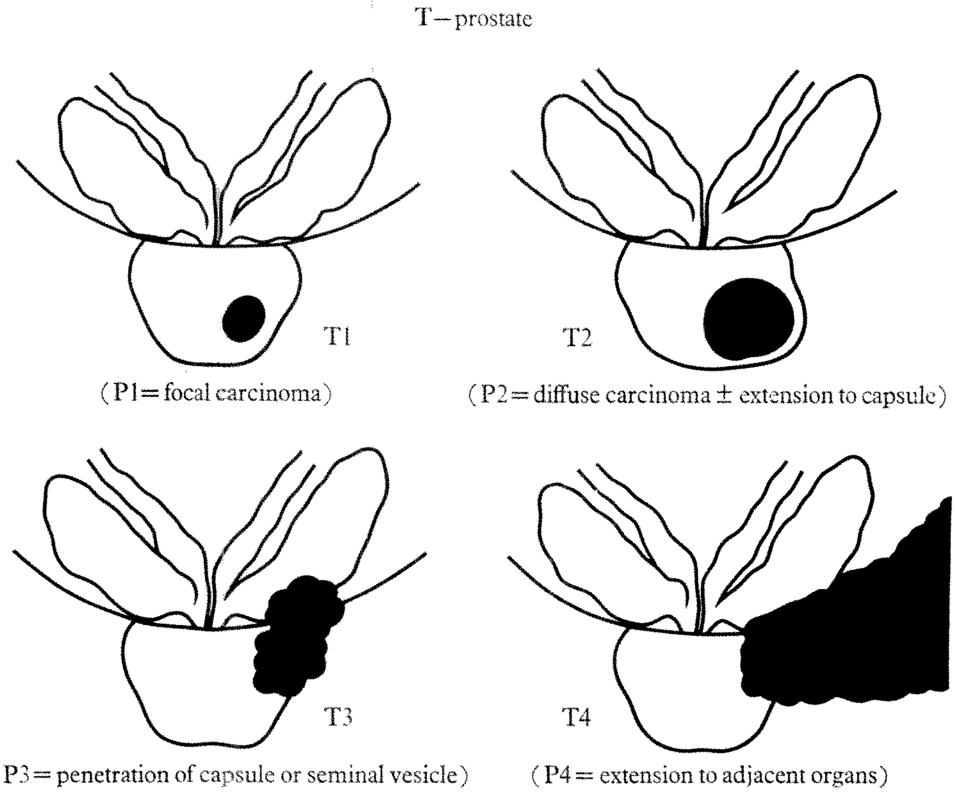
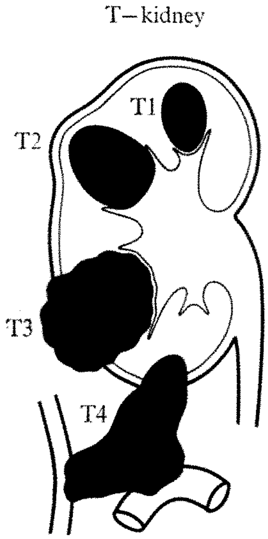

T—prostate
T1
(P1 = focal carcinoma)
T2
(P2 = diffuse carcinoma ± extension to capsule)
T3
(P3 = penetration of capsule or seminal vesicle)
T4
(P4 = extension to adjacent organs)

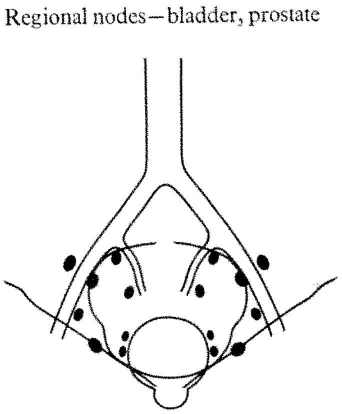
Fig. 2. T/P classification for prostate. T0—no tumour palpable; T1—nodule in palpably normal gland; T2—smooth nodule deforming contour of gland; T3—tumours extending beyond capsule, or into seminal vesicles, T4—fixed (see Appendix for details).

Prostate. T—The primary tumour. The behaviour of prostatic lesions has been difficult to study because not all so-called carcinomas of the prostate have been proved by histology to be malignant. Before assessing any prostatic tumour it is essential that there is histological or cytological proof that the lesion is in fact malignant. The description of a prostatic tumour is also difficult because it depends largely on the feel of the posterior surface of the gland. It can be difficult to assess mobility because of the normal limitation on mobility due to the puboprostatic laigments. Not every patient is cytoscoped and so involvement of the bladder may not be recorded. Clinically unsuspected carcinoma, discovered incidentally in a prostatectomy specimen, should be classified T0. When the minimum requirements cannot be met—for example, after abdomino-perineal resection of rectum—the symbol TX should be used. T1-4 are described in the appendix, and are illustrated in Figure 2.

Kidney. T—The primary tumour. The assessment of the clinical spread of a primary tumour in the kidney is extremely difficult. Some patients may be fat, some patients thin. In some, it may be possible to feel the kidney, in others there may be merely a fullness in the renal fossa. It was agreed that the extent of the tumour can only be accurately determined by means of arteriography, and the appended classification has been proposed for evaluation for the trial period (Fig. 3).

The extent of venous invasion in kidney tumours determined by venography and/or by examination of the pathological specimen has been classified as follows:





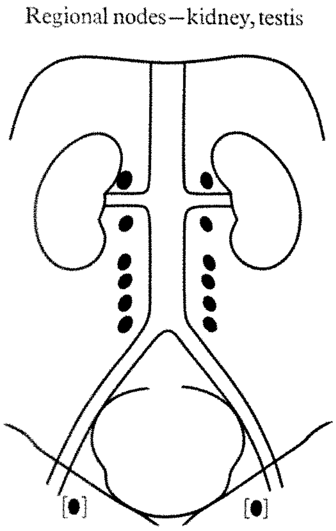


Fig. 3. T/P classification for kidney—based on arteriography. T1—small tumour without enlargement of kidney; T2—large tumour with enlargement or deformity of kidney—continuity of cortex preserved; T3—spread into perinephric fat; T4—invasion into adjacent organs or abdominal wall; TX—arteriography not performed (see Appendix for details).

Fig. 4. Regional nodes (= N) for bladder and prostate: nodes within the pelvis below the bifurcation of the common iliac arteries (see Appendix for details).

Fig. 5. Regional nodes (= N) for kidney and testis: para-aortic and paracaval nodes; ipsilateral inguinal nodes only after scrotal interference with testicular tumours (see Appendix for details).

VX The extent of invasion cannot be assessed.
V0 The veins do not contain tumour.
V1 Renal vein contains tumour.
V2 Vena cava contains tumour.

Testis T—The primary tumour. Since the extent of the primary tumour is difficult to assess clinically, evidence derived from orchidectomy (which in this case is considered as a biopsy) is used to establish the T category.

The Pathological Aspects

It is essential that all patients who are treated for tumours should have a positive microscopic evidence of malignancy. It may well be that in the past many patients have been treated without histological confirmation and it is possible that the condition for which they were treated was not in fact neoplastic. It is mandatory that there is proof of malignancy, and this proof may be either from a biopsy or based on cytology.

At all sites the depth of invasion as assessed by the examination of the *operative* specimen has the same numerical values as the clinical assessment but is preceded by the symbol P. Histopathological grading may now be included with the initial T.N.M. classification of the tumour. For the bladder, this grading should conform to the recommendations of W.H.O. (1973).

Microscopic evidence of lymphatic invasion in the bladder may be classified with the symbol L, as shown in the appendix.

Regional and Juxtaregional Nodes = N

The regional nodes for the 4 urogenital sites are of course different. The regional nodes for the bladder and prostate (Fig. 4) are those within the pelvis and below the bifurcation of the common iliac arteries. Nodes above this level along the common iliac arteries or in the para aortic area are considered for the bladder and prostate to be juxta-regional nodes. The testes and kidney drain to the para aortic nodes (Fig. 5) on one or both sides below the diaphragm and these nodes are considered regional. Nodes above the diaphragm or below the bifurcation of the aorta are considered to be juxta-regional. Lymphography is mandatory, and if this evidence is not available, the symbol NX should be used. Where the nodes appear normal, they are classified N0. Evidence of node involvement is classified as follows:

N1 Involvement of a single homolateral lymph node.
N2 Involvement of contralateral *or* bilateral *or* multiple regional lymph node.
N3 There is a fixed mass on the pelvic wall with a free space between this and the tumour.
N4 Involvement of juxta-regional lymph nodes.

Metastases = M

Metastases are indicated by the symbol M. This is a conventional symbol but the subgroups have been standardised for all urological sites. M0 means no evidence on clinical or radiological studies of metastatic disease. M1 has been divided into subgroups so that different forms of spread can be compared. This subdivision, which adds to the complexity, must remain optional.

M0 No evidence of metastases.
M1 Distant metastases present.
M1a Evidence of occult metastases by biochemical and/or other tests.
M1b Single metastases in a single organ site.
M1c Multiple metastases in a single organ site.
M1d Metastases in multiple organ sites.

Future Extension of the T.N.M. System

Although the T.N.M. system has been extended to include additional facts for urological tumours (*e.g.* grade, venous and lymphatic invasion), further categories may need to be added in the future. The anatomico-pathological approach could be supplemented by a functional assessment, by the measurement of marker substances such as alpha-foeto-protein or antigens, or by measurement of immunological responses. Such indices may be added easily to the T.N.M. system and their value in prognosis compared with more conventional systems.

In brief, the basic concept of the T.N.M. system has been extended by adding other symbols —P for the pathological report of an operative specimen, G for the grade, L for lymphatic vessel involvement, or V for evidence of venous invasion. The possibility of adding such measurements as biochemical markers keeps the system adaptable and capable of expansion.

We wish to thank Mr Michael H. Harmer, Chairman of the T.N.M. Committee of the U.I.C.C., for his assistance in the preparation of this paper and for permission to reproduce the T.N.M. Classification for Urological Tumours. We wish also to thank the Medical Art Department at the Royal Marsden Hospital for the illustrations, and Miss Anthea Minchom, who prepared the typescript.

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Appendix

Introductory Notes to the Classification of Urinary Sites

The development of classification for deep-seated tumours poses very different problems from those which apply to the superficial or accessible areas.

The 4 sites which are included in this section, namely bladder, prostate, kidney and testis have their specific problems but can be classified according to a common plan. Certain modifications to the hitherto accepted rules of the T.N.M. system are however necessary to do so.

In the first place, minimum requirements for the meaningful categorisation of a primary tumour, the lymph nodes and metastases are necessary. For instance, arteriography and lymphography may be mandatory. It is recognised that such facilities are not uniformly available and clinicians who do not have them at their disposal cannot classify these tumours according to the system proposed.

Secondly, it is now recognised that the lymph nodes beyond the regional (or "first station") nodes may be treated and so these juxtaregional (or "second station") nodes are also classified.

Thirdly, in the case of tumours of the testis, when radical orchidectomy is performed for confirmation of the diagnosis, this provides the necessary information for assessment of the extent of the primary tumour.

The following classifications should therefore be approached with these facts in mind since they appear to depart from previously accepted classifications.

It must be emphasised that these are not definitive classifications. Though based on the experience of a large international group of urologists, radiotherapists and pathologists, and supported by considerable data, they *have not yet been fully tested in field trials.* It is considered that the only way this can be done is by publication so that they may be tested by clinicians as widely as possible.

BLADDER

Rules for Classification

The classification applies only to epithelial tumours. Papilloma is excluded but such cases may be listed under the category GO. There must be histological or cytological verification of the disease.

The following are the minimum requirements for assessment of the T, N and M categories. If these cannot be met the symbol TX, NX or MX will be used.

T categories:	Clinical examination, urography, cystoscopy, bimanual examination under full anaesthesia and biopsy or transurethral resection of the tumour (if indicated) prior to definitive treatment.
N categories:	Clinical examination, lymphography and urography.
M categories:	Clinical examination, chest X-ray and biochemical tests. In the more advanced primary tumours or when clinical suspicion warrants, radiographic or isotope studies should be done.

T.N.M. Classification

T—Primary Tumour

The suffix (m) may be added to the appropriate T category to indicate multiple tumours *e.g.* T2(m)

TIS Pre-invasive carcinoma (carcinoma *in situ*)
TX The minimum requirements to assess fully the extent of the primary tumour cannot be met.

T0 No evidence of primary tumour.
T1 On bimanual examination a freely mobile mass may be felt: this should not be felt after complete transurethral resection of the lesion *and/or*
Microscopically the tumour does not extend beyond the lamina propria.

Note: This category includes papillary tumours (both infiltrating and non-infiltrating).

T2 On bimanual examination there is induration of the bladder wall which is mobile. There is no residual induration after complete transurethral resection of the lesion *and/or*
There is microscopic invasion of superficial muscle.
T3 On bimanual examination induration *or* a nodular mobile mass is palpable in the bladder wall which persists after transurethral resection of the exophytic part of the lesion *and/or*
There is microscopic invasion of deep muscle or of extension through the bladder wall.
  T3a Invasion of deep muscle.
  T3b Extension through the bladder wall.
T4 Tumour fixed or invading neighbouring structures *and/or*
There is microscopic evidence of such involvement.
  T4a Tumour invading prostate, uterus or vagina.
  T4b Tumour fixed to the pelvic wall *and/or* infiltrating the abdominal wall.

N—Regional and Juxta-regional Lymph Nodes

The regional lymph nodes are the pelvic nodes below the bifurcation of the common iliac arteries. The juxta-regional nodes are the inguinal nodes, the common iliac and para-aortic nodes.

NX The minimum requirements to assess the regional lymph nodes cannot be met.
N0 No evidence of involvement of regional lymph nodes.
N1 Involvement of a single homolateral regional lymph node.
N2 Involvement of contralateral *or* bilateral *or* multiple regional lymph nodes.
N3 There is a fixed mass on the pelvic wall with a free space between this and the tumour.
N4 Involvement of juxta-regional lymph nodes.

Subsequent information regarding the histological assessment of the regional lymph nodes may be added to the clinical N category thus: N− (minus) for nodes with no microscopic evidence of metastases; or N+ (plus) for nodes with microscopic evidence of metastases, *e.g.* N0+, N1−.

M—Distant Metastases

MX The minimum requirements to assess the presence of distant metastases cannot be met.
M0 No evidence of distant metastases.
M1 Distant metastases present.
  M1a Evidence of occult metastases based on biochemical *and/or* other tests.
  M1b Single metastases in a single organ site.
  M1c Multiple metastases in a single organ site.
  M1d Metastases in multiple organ sites.

Note: the location of metastases should be specified. The lymph nodes beyond the regional and juxta-regional nodes, and bone are regarded as single organ sites.

P—Histopathological Categories

Assessment of the P categories is based on evidence derived from surgical operation and histopathology—*i.e.* where tissue other than biopsy is available for examination.

The suffix (m) may be added to the appropriate P category to indicate multiple tumours, *e.g.* P2(m).

P1S Pre-invasive carcinoma (carcinoma *in situ*).
PX The extent of invasion cannot be assessed.
P0 No tumour found on examination of specimen.
P1 Tumour not extending beyond the lamina propria.
P2 Tumour with infiltration of superficial muscle (not more than half-way through muscle coat).
P3 Tumour with infiltration of deep muscle (more than halfway through muscle coat) *or* infiltration of perivesical tissue.
P4 Tumour with infiltration of prostate or other extravesical structures.

G—Histopathological Grading

GX Grade cannot be assessed.
G0 No evidence of anaplasia, *i.e.* papilloma.

G1 Low grade malignancy.
G2 Medium grade malignancy.
G3 High grade malignancy.

L—Invasion of Lymphatics

LX Lymphatic invasion cannot be assessed.
L0 No lymphatic invasion.
L1 Superficial lymphatics invaded.
L2 Deep lymphatics invaded.

Note: the histopathological categories and grading conform to the recommendations of W.H.O. Ref.: Histological Typing of Urinary Bladder Tumours, W.H.O., 1973, Geneva.

Stage—Grouping

A stage grouping is not at present recommended.

PROSTATE

Rules for Classification

The classification applies only to carcinoma.

There must be histological or cytological verification of the disease, to permit division of cases by histological type.

The following are the minimum requirements for assessment of the T, N and M categories. If these cannot be met the symbol TX, NX or MX will be used.

T categories: Clinical examination, urography, endoscopy and biopsy (if indicated) prior to definitive treatment.
N categories: Clinical examination, lymphography *and/or* urography.
M categories: Clinical examination, chest X-ray, skeletal studies and determination of the acid phosphatase level on two or more occasions.

T.N.M. Classification

T—Primary Tumour

The suffix (m) may be added to the appropriate T category to indicate multiple tumours—*e.g.* T2(m).

TX The minimum requirements to assess fully the extent of the primary tumour cannot be met.
T0 No tumour palpable. This category includes those cases of the incidental finding of a Ca. in an operative or biopsy specimen. Such cases should be assigned an appropriate P, N or M category.
T1 Tumour intracapsular surrounded by palpably normal gland.
T2 Tumour confined to the gland. Smooth nodule deforming contour but lateral sulci and seminal vesicles not involved.
T3 Tumour extending beyond the capsule with or without involvement of the lateral sulci *and/or* seminal vesicles.
T4 Tumour fixed or invading neighbouring structures.

N—Regional and Juxta-Regional Lymph Nodes

The regional lymph nodes are the pelvic nodes below the bifurcation of the common iliac arteries. The juxta-regional nodes are the inguinal nodes, the common iliac and para-aortic nodes.

NX The minimum requirements to assess the regional lymph nodes cannot be met.
N0 No evidence of involvement of regional lymph nodes.
N1 Involvement of a single regional lymph node.
N2 Involvement of multiple regional lymph nodes.
N3 There is a fixed mass on the pelvic wall into a free space between this and the tumour.
N4 Involvement of juxta-regional nodes.

Subsequent information regarding the histological assessment of the regional lymph nodes may be added to the clinical N category thus: N− (minus) for nodes with no microscopic evidence of metastasis; or N+ (plus) for nodes with microscopic evidence of metastasis, *e.g.* N0+, N1−.

M—Distant Metastases

If lymphography indicates extension to the juxta-regional nodes a scalene node biopsy is recommended.

MX The minimum requirements to assess the presence of distant metastases cannot be met.

M0 No evidence of distant metastases.
M1 Distant metastases present.
  M1a Evidence of occult metastases by biochemical *and/or* other tests.
  M1b Single metastasis in a single organ site.
  M1c Multiple metastases in a single organ site.
  M1d Metastases in multiple organ sites.
  Note: The location of metastases should be specified. The lymph nodes beyond the regional and juxta-regional nodes, and bones are regarded as single organ sites.

P—Histopathological Categories

Assessment of the P categories is based on available material whether biopsy, trans-urethral resection, enucleation or total prostatectomy: the source to be stated.

The suffix (m) may be added to the appropriate P category to indicate multiple tumours, *e.g.* P2(m).

PX The extent of invasion cannot be assessed.
P0 No tumour found on examination of specimen.
P1 Focal (single or multiple) carcinoma.
P2 Diffuse carcinoma with or without extension to the capsule.
P3 Carcinoma with penetration through the capsule *and/or* extension to the seminal vesicles.
P4 Extension into adjacent organs.

G—Histopathological Grading

GX Grade cannot be assessed.
G0 No evidence of anaplasia.
G1 Low grade malignancy.
G2 Medium grade malignancy.
G3 High grade malignancy.

Stage—Grouping

A stage grouping is not at present recommended.

KIDNEY

Rules for Classification

The classification applies only to renal-cell carcinoma. Adenoma is excluded but such cases may be listed under the category G0.

There must be histological or cytological verification of the disease. Any unconfirmed cases must be reported separately.

The following are the minimum requirements for assessment of the T, N and M categories. If these cannot be met the symbol TX, NX or MX will be used.

T categories: Clinical examination, urography and arteriography prior to definitive treatment.
N categories: Clinical examination, lymphography and urography.
M categories: Clinical examination, chest X-ray and biochemical tests. In the more advanced primary tumours or when clinical suspicion warrants, radiographic or isotope studies should be done.

T.N.M. Classification

T—Primary Tumour

In the absence of arteriography, the symbol TX must be used.

TX The minimum requirements to assess fully the extent of the primary tumour cannot be met.
T0 No evidence of primary tumour.
T1 Evidence of a small tumour without enlargement of the kidney. There is a limited calyceal distortion or deformity and circumscribed vascular deformities, surrounded by renal parenchyma.
T2 Evidence of a large tumour with deformity *and/or* enlargement of the kidney or calyceal or pelvic involvement. The continuity of the cortex is preserved on arteriography.
T3 Evidence of spread into perinephric fat, peri-pelvic fat or hilar renal vessels.
T4 Evidence of invasion into neighbouring organs or abdominal wall.

N—Regional and Juxta-Regional Lymph Nodes

The regional lymph nodes are the para-aortic and para-caval nodes. The juxta-regional nodes are the intrapelvic nodes and the mediastinal nodes.

NX The minimum requirements to assess the regional lymph nodes cannot be met.
N0 No evidence of involvement of regional lymph nodes.
N1 Involvement of a single homolateral regional lymph node.
N2 Involvement of contralateral *or* bilateral *or* multiple regional lymph nodes.
N3 Fixed regional lymph nodes (assessable only at surgical exploration).
N4 Involvement of juxta-regional lymph nodes.

Subsequent information regarding the histological assessment of the regional lymph nodes may be added to the clinical N category thus: N− (minus) for nodes with no microscopic evidence of metastasis; or N+ (plus) for nodes with microscopic evidence of metastasis, e.g. No+, N1−.

M—Distant Metastases

MX The minimum requirements to assess the presence of distant metastases cannot be met.
M0 No evidence of distant metastases.
M1 Distant metastases present.
  M1a Evidence of occult metastases based on biochemical *and/or* other tests.
  M1b Single metastases in a single organ site.
  M1c Multiple metastases in a single organ site.
  M1d Metastases in multiple organ sites.
  Note: The location of metastases should be specified. The lymph nodes beyond the regional and juxta-regional nodes, and bone are regarded as single organ sites.

P—Histopathological Categories

Assessment of the P categories is based on evidence derived from surgical operation and histopathology—*i.e.* where tissue other than biopsy is available for examination.

PX The extent of invasion cannot be assessed.
P0 No primary renal-cell tumour found on examination of specimen.
P1 Tumour surrounded by renal parenchyma.
P2 Tumour extending to the capsule *and/or* invading the renal pelvis *and/or* calyces.
P3 Tumour extending beyond the capsule into the perinephric fat *or* the peripelvic fat *or* the renal pedicle.
  P3a Extension to perinephric fat.
  P3b Extension to peripelvic fat.
  P3c Extension to renal pedicle.
P4 Tumour invading neighbouring organs *and/or* fixed to the abdominal wall.

V—Invasion of Veins

VX The extent of invasion cannot be assessed.
V0 The veins do not contain tumour.
V1 Renal vein contains tumour.
V2 Vena cava contains tumour.

G—Histopathological Grading

GX Grade cannot be assessed.
G0 No evidence of anaplasia, *i.e.* adenoma.
G1 Low grade malignancy.
G2 Medium grade malignancy.
G3 High grade malignancy.

Stage—Grouping

A stage grouping is not at present recommended.

TESTIS

Rules for Classification

Testis refers to the body of the testis and excludes the epididymis.

There must be histological verification of the disease. Cases must be divided by histological type. Malignant lymphoma is excluded.

The following are the minimum requirements for assessment of the T, N and M categories. If these cannot be met the symbol TX, NX or MX will be used.

T categories: Clinical examination and radical orchidectomy which in this case is considered as a biopsy.
N categories: Clinical examination, lymphography and urography.
M categories: Clinical examination, chest X-ray and biochemical test.

T.N.M. Classification

T—Primary Tumour

In the absence of orchidectomy the symbol TX must be used.

TX The minimum requirements to assess fully the extent of the primary tumour cannot be met.
T0 No evidence of primary tumour.
T1 Tumour limited to the body of the testicle.
T2 Tumour extending beyond the tunica albuginea.
T3 Tumour involving the rete testis or epididymis.
T4 Tumour invading the spermatic cord or scrotal wall.
  T4a Invasion of the spermatic cord.
  T4b Invasion of the scrotal wall.

N—Regional and Juxta-Regional Lymph Nodes

The regional lymph nodes are the para-aortic and para-caval nodes. Following scrotal surgery the homolateral inguinal lymph nodes are included with the regional lymph nodes. The juxta-regional nodes are the intrapelvic nodes, and the mediastinal and supraclavicular nodes.

NX The minimum requirements to assess the regional lymph nodes cannot be met.
N0 No evidence of involvement of regional lymph nodes.
N1 Involvement of a single homolateral regional lymph node, which, if inguinal, is mobile.
N2 Involvement of contralateral *or* bilateral *or* multiple regional lymph nodes, which, if inguinal, are mobile.
N3 A palpable abdominal mass is present *or* there are fixed inguinal lymph nodes.
N4 Involvement of juxta-regional nodes.

Subsequent information regarding the histological assessment of the regional lymph nodes may be added to the clinical N category thus: N− (minus) for nodes with no microscopic evidence of metastasis; or N+ (plus) for nodes with microscopic evidence of metastasis, *e.g.* N0+, N1−.

M—Distant Metastases

As the primary tumour advances or if clinical suspicion warrants, skeletal or isotope studies should be done.

MX The minimum requirements to assess the presence of distant metastases cannot be met.
M0 No evidence of distant metastases.
M1 Distant metastases present.
  M1a Evidence of occult metastases based on biochemical *and/or* other tests.
  M1b Single metastases in a single organ site.
  M1c Multiple metastases in a single organ site.
  M1d Metastases in multiple organ sites.
  Note: The location of metastases should be specified. The lymph nodes beyond the regional and juxta-regional nodes, and bone are regarded each as single organ sites.

P—Histopathological Categories

Assessment of the P categories is based on evidence derived from surgical operation and histopathology following orchidectomy.

The P categories correspond to the T categories.

P0 No evidence of primary tumour.
P1 Tumour limited to the body of the testis.
P2 Tumour extending beyond the tunica albuginea.
P3 Tumour invading the rete testis *and/or* epididymis.
P4 Tumour invading the spermatic cord *and/or* scrotal wall.
  P4a Invasion of spermatic cord.
  P4b Invasion of scrotal wall.

Stage—Grouping

A stage grouping is not at present recommended.

British Journal of Urology (1975), **47**, 13–16

The Staging of Renal Parenchymal Tumours

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The original T.N.M. System of clinical staging proposed by the Union Internationale Contre Cancer (U.I.C.C. 1968) was not applicable to renal parenchymal tumours, because the 3 principal clinically demonstrable parameters were not of reliable significance.

(*a*) The *size* is of very limited value for staging and for prognosis.
(*b*) The *urographic distortion* can be very slight in a very advanced tumour on the one hand or very marked in a very benign tumour.
(*c*) The *mobility* can be a decisive factor only if it is definitely limited or it is fixed.

It is very doubtful if a solely clinical classification into T1-T4 is possible at all. However, the arteriographic changes could be used as a factor in prognosis, and the *histological grading* is certainly of value in estimating the prognosis (Riches, Griffiths and Thackray, 1951).

Tumour Size

In our series of 200 renal parenchymal tumours, the prognosis was related to the volume as in Table I.

The size has therefore some importance, but is far from being a reliable factor.

Table I

Value of Tumours and Prognosis

		Died (years)			
Volume	Patients	0-1	1-3	3-5	Alive >5 years
−5 cm	15	2	4	—	9 (60%)
5-10 cm	77	16	23	4	34 (44%)
10+ cm	95	54	17	5	19 (20%)
Unknown	13				
	200				

Number of Tumours

A solitary tumour has a better prognosis than multiple tumours (Table II).

The Pseudocapsule of the Tumour

This is complete only occasionally. In our 200 cases it existed in only 18 (9%), but this is a very important factor reflecting a limit in the advancement of the tumour. This pseudocapsule is an expression of the compression as opposed to the invasion of the surrounding tissues; if the capsule is complete, the invasion by the tumour is almost certainly limited. In our classification this completeness of the capsule is a condition *sine qua non* for its being put in Stage A.

Of our 18 cases we have 14 (77%) surviving more than 5 years and 7 are alive at more than 10 years.

Table II

Number of Tumours and Prognosis

		Died (years)			
Tumour	Patients	0-1	1-3	3-5	Alive > 5 Years
Solitary	50	9	3	5	33 (66%)
Multiple	123	60	27	8	28 (23%)
Unknown	27				
	200				

From the moment this capsule is broken or if it never existed, metastases may occur irrespective of the size of the tumour.

Perirenal Adhesions

This finding is a reliable feature in showing a fibrous (biological) reaction. When absent or very limited the finding does not preclude a very good prognosis because a highly malignant tumour can progress without producing adhesions and a very large benign tumour can be present for a long time without the development of adhesions. The absence of adhesions is not a reliable sign of an early stage, but taken as a whole it is of rather good import (Table III).

Table III

Perirenal Adhesions and Prognosis

		Died (years)			
Adhesions	Patients	0-1	1-3	3-5	Alive 5 Years
Absent or minimal	77	11	13	7	46 (60%)
Marked	123	63	26	9	15 (12%)
	200				

Involvement of the Renal Capsule

The significance of this factor was considered by Beare and McDonald (1949), who reported a poor prognosis after involvement of the fatty capsule but not with involvement of only the renal fibrous capsule. The findings in our 200 cases are shown in Table IV.

Renal Vein Involvement

The finding of involvement of the renal vein by tumour is a very controversial feature. By many authors it is considered to be particularly characteristic of progression and a decisive factor in staging. It certainly worsens the prognosis of renal tumours, but it is only a minor factor. Riches, Griffiths and Thackray had a 5 years and 10 years survival without renal vein involvement in 58% and 32%, and with this involvement in 27% and 20% respectively. McDonald and Priestley (1943) had a 5 years survival in 29% with renal vein involvement and in 55·4% without renal

Table IV

Involvement of Renal Capsule and Prognosis

		Died (years)			
Renal Capsule	Patients	0-1	1-3	3-5	Alive 5 Years
Unperforated	100	17	18	8	57 (57%)
Perforated	84	51	18	7	8 (10%)
Unknown	16				
	200				

Table V

Stage and Prognosis in Cases with Renal Vein Involvement

		Died (years)			Alive (years)	
Stage	Patients	0-1	1-3	3-5	5>	10>
B	5		1		3	1
C	14	5	3	1	3	2
D	2					
	21					

vein involvement. Robson, Churchill and Anderson (1969), report a better prognosis finding 8 out of 13 patients surviving 3 to 7 years with renal vein involvement. Even vena cava involvement need not be associated with early death; we have 2 patients out of 6 surviving 5 years. The survival of our 21 cases with renal vein involvement, depending on the stage (see our classification below) shown in Table V.

In all (43%) out of 21 cases survived more than 5 years after operation.

Lymph Node Involvement

This certainly worsens the prognosis. Flocks and Kadesky (1958), found a 5 years survival in 3 (14%) out of 21 cases. Skinner, Vermillion and Colvin (1972) found it in 15%. In our 200 cases we have 43 patients with lymph node involvement and only 3 (7%) survived 5 years. The distribution of survival in a group of the same stage (C) with or without lymph node involvement are shown in Table VI.

Our Classification

We proposed in 1956 (Petković, 1956) the following classification of stages of renal tumour extension:

Stage A. Intracapsular stage. The tumour must have its own pseudocapsule complete (*i.e.* no perforation). **Stage B.** The tumour invasion is confined to the kidney tissue; it is not outside the kidney. **Stage C.** The tumour has some signs of involvement of surrounding structures such as perforation of the fibrous capsule and perirenal invasion, lymph node involvement or renal vein involvement—but N.B., we no longer attach this degree of importance to renal vein involvement. **Stage D.** Distant metastases are present.

The value of this anatomical classification can be seen from our 200 cases followed for more than 5 years after operation (Table VII).

Stage A has an excellent prognosis and Stage B has a fairly good prognosis. Stage A allows us to consider the possibility of limited operation by enucleation.

Table VI

Lymph Node Involvement and Prognosis

		Died (years)			
Involvement	Patients	0-1	1-3	3-5	Alive 5 > Years
Yes	43	27	10	3	3 (7%)
No	80	41	21	3	15 (19%)
	123				

Table VII

Author's Staging and Prognosis

		Died (years)				
Stage	Patients	0-1	1-3	3-5	Alive > 5 Years	?
A(I)	18	0	1	3	14 (77%)	—
B(II)	51	7	12	1	31 (60%)	—
C(III)	123	64	31	6	16 (13%)	4
D(IV)	8	7	1	—		
	200	78	45	10	63 (31%)	4

Summary

The relation between the anatomical features in the development of renal parenchymal tumours and the prognosis are analysed. It is suggested that the clinical and anatomical classification must be revised.*

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**Editor's note:* Professor Petković presented these recommendations to the T.N.M. committee of the U.I.C.C. in May 1974, and his proposals were used as a basis for the classification which is published in full on p. 1.

British Journal of Urology (1975), **47**, 17–24

Determination of the Optimum Temperature for Regional Renal Hypothermia during Temporary Renal Ischaemia

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With the advent of increasing skills in the techniques of conservative renal surgery, the surgeon has been tempted to render the kidney ischaemic for long periods exposing it to the risk of severe nephron injury. In the last 15 years since the introduction of the technique of regional renal hypothermia, prolonged ischaemia times have become possible, enabling complex operative procedures without the concomitant parenchymal damage normally associated with prolonged renal ischaemia. The temperature at which the *in situ* kidney should be maintained while it is ischaemic is open to speculation and debate. The increasing use of hypothermia, together with the uncertainty of the optimum temperature, make its accurate determination extremely important.

Severe parenchymal injury occurs following prolonged ischaemia at 37°C and similar damage results from the effects of freezing at 0°C and below. The optimum temperature lies somewhere between these two values, where cooling affords protection during ischaemia, yet where the renal tissues are not damaged by cold.

Evidence of cold injury to renal cells by temperatures above 0°C has been described by Mitchell and Woodruff (1957), Birkeland *et al.* (1959), Kiser *et al.* (1961), Mirkovitch and Chassot (1970) and Grana, Donnellan and Swenson (1971), the brush borders of the proximal convoluted tubules being the first structures destroyed. Fats have been shown to solidify at 15°C and lipoproteins become unstable and in their isolated renal perfusion studies Belzer *et al* (1968) showed that lipid denaturation occurred at about this temperature causing rising perfusion pressure and capillary blockage, hence the use of his cryoprecipitated millipore filtered plasma.

Since the demonstration in 1956 by Bogardus and Schlosser and by Birkeland *et al.* (1959), of the use of *in situ* renal hypothermia in experimental animals, many surgeons have applied these techniques to renal surgery in man. Well over 1,000 such operations have been reported in the literature from over 20 centres (see Table I). The choice of temperature has been empirical, varying from near 0° to 32°C.

There have been 6 specific attempts to find the optimum temperature for the ischaemic *in situ* kidney which have yielded results varying from near 0° to 25°C (see Table II). In 4 of these experiments only the plasma creatinine and the blood urea nitrogen (BUN) together with the survival of the animal have been the parameters by which renal function has been measured. The main drawback to this approach is the large number of experimental variables inherent in the whole animal survival model when single organ function is being studied. For example, Fegen, Albert and Persky (1970) arrived at an optimum renal temperature for previously unilaterally nephrectomised rats undergoing renal pedicle occlusion by observing that all those whose kidney was cooled to 0° to 5°C survived. However, all those cooled to 10° to 15°C also survived and it was only the higher BUN and creatinine of the latter group which enabled them to conclude that 0 to 5 was the optimum temperature. This is indeed a crude measure of renal function. The

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June, 1974.

Table I

Regional Renal Hypothermia in Man

Year	Country	Investigators	Operation	Number	Kidney Temperature
1956	Norway	Birkeland *et al.*	Partial nephrectomy	3	5° to 10°C
1957	USA	Goodwin	Segmental resection	1	Probably 5° to 25°C
1959	Norway	Semb	Calculus or TB	4*	23°C
1959	Canada	Wilson	Calculus or TB	4	Aimed at 20°C
1960	England	Stewart	Partial nephrectomy	41	*s* 21°C, *c* 25°C
1960	Canada	Kerr *et al.*	Calculi	15	*s* 15° to 25°C, *c* 22° to 32°C
1960	USA	Cockett	Heminephrectomy or calculi	6	*c* 16° to 20°C
1963	Canada	Wilson	Calculi, TB or cyst	22*	12° to 31°C, mean core 22°C
1963	USA	Palmer *et al.*	Calculi	2	2° to 24·5°C
1963	England	Graves	Calculi, TB or partial nephrectomy	10	21°C
1964-69	USSR	Ovnatanjan	Calculi, TB or cyst	135	10° to 25°C
1967	England	Wickham *et al.*	Calculi	20	Aimed at 20°C
1968	England	Hanley *et al.*	Calculi	22*	Aimed at 20°C
1968	USSR	Lopatkin *et al.*	Calculi	300+	
1969	USSR	Aivazyan	Calculus or TB	2	0° to 20°C
1971	USSR	Ovnatanjan	Calculi	9	10° to 25°C
1971	USSR	Schioschwili	Calculi	20	20° to 25°C
1971	England	Wickham *et al.*	Calculi	50	20° to 25°C
1960-72	USA	Metzner *et al.*	Calculi, vascular disease, etc.	300+	*s* 5°C, *c* aimed at 20°C
1974	England	Wickham *et al.*	Calculi	100	20° to 25°C

* Probably include cases they have previously reported. *s* = Surface temperature. *c* = Core temperature.

Table II

Specific Attempts to find the Optimum Temperature using Local Hypothermia

Year	Investigators	Animal	Pedicle or Artery	Ischaemia Time	Optimum Temperature
1957	Mitchell and Woodruff	Sheep	p	2 hr	10° to 20°C
1959	Mitchell	Lambs	p	1½ to 2 hr	10° to 20°C
1958	Stueber *et al.*	Dogs	p	6 hr	0° to 5°C
1959	Birkeland and Vogt	Dogs	a	up to 12 hr	5° to 17°C
1966	Wickham	Rabbits	a	45 min	5° to 30°C 20° to 25°C advised
1970	Fegen, Albert and Persky	Rats	a	3 hr	0° to 5°C
1971	Schioschwili	Dogs	a	2 hr	20° to 25°C

length of ischaemia time is also very significant. When Stueber *et al.* (1958) found the optimum temperature to be 0° to 5°C, his canine renal ischaemia time was 6 hours, whereas other workers were investigating 1½ to 3 hours ischaemia, and it may be that the rate of consumption of oxygen is the critical factor in longer ischaemic periods.

Objective

Specific methods of measurement must be included in the design of an experiment so as to differentiate small changes in renal function and renal cell injury. Therefore the glomerular filtration rate (GFR), the renal tubular function, the renal blood flow and plasma and urine enzyme release should be studied before and after ischaemia to elucidate the optimum level of hypothermia. The ischaemia time should compare with that used in conservative renal surgery in man, approximately 90 minutes. These parameters and conditions are included in the following experiment.

Methods

47 adult mongrel dogs were anaesthetised with sodium pentobarbital and respired by positive pressure ventilation and cannulated as shown in Figure 1. The abdomen was opened, the left ureter cannulated and after 3 control renal function measurements, the kidney was dissected free from its peritoneal attachments until freely mobile and the renal artery was cross clamped.

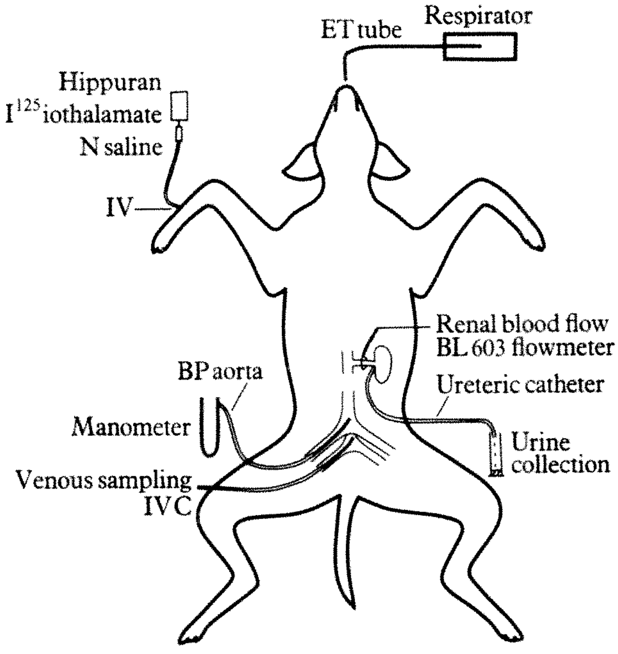


Fig. 1.

35 of these were divided into groups of 5 and underwent 90 minutes of left renal ischaemia with the kidney temperature maintained at 37°, 30°, 22°, 15°, 10°, 5° and 0°C respectively, using an insulated renal cooling coil (Fig. 2) and a high flow thermostatically controlled cooling apparatus (Fig. 3). The renal temperature was measured by 2 telethermometer probes 2 cm into the renal substance. 7 dogs were studied in a preliminary experiment so that a technique was developed where conditions were standardised so that the only variable factor in each group of subsequent dogs was the temperature of the kidney. 5 further dogs underwent special isotope and radiographic studies.

The glomerular filtration rate was measured by ^{125}I labelled sodium iothalamate as described by Anderson, Sawyer and Cutler (1968) and tubular function by the maximal tubular capacity for secretion of para-aminohippuric acid (TmPAH) using chemical estimation of PAH, following a 30-minute stabilisation period, both before and at regular 15-minute intervals after the ischaemic period. Background substracted isotope counts were performed in an Autowell scintillation counter. The renal artery blood flow was measured using a clinical blood flow meter with an encircling flow probe both before and after the ischaemia. Renal arteriograms were performed, as were

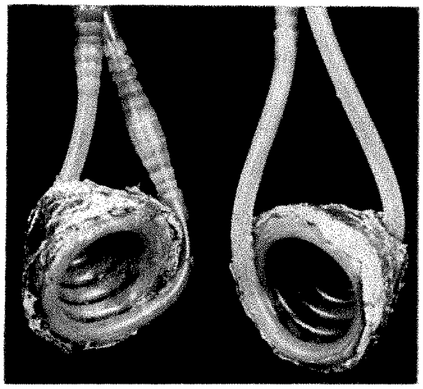


Fig. 2. Insulated renal cooling coils.

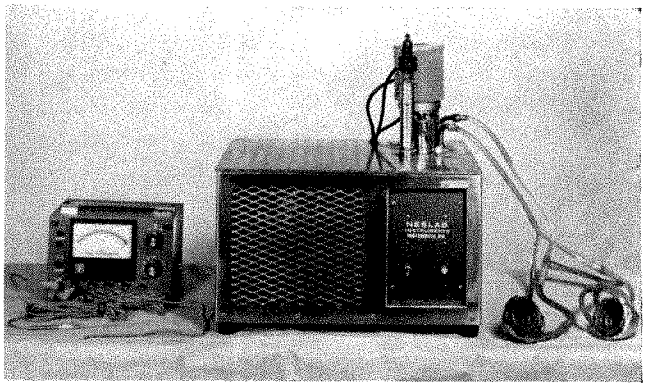


Fig. 3. High flow, thermostatically controlled cooling apparatus.

the release into the plasma of lactic dehydrogenase, its isozymes and γ-glutamyl transpeptidase. The urinary activity of γ-glutamyl transpeptidase was measured in all 35 dogs undergoing renal ischaemia at each temperature range. Chromium-51 labelled platelets of the same dog were injected in an attempt to observe platelet thrombi occurring in the ischaemically injured kidney. Histological examination of the kidneys was performed.

Results

The relative efficiency of the cooling coil apparatus is shown in Figure 4, 15°C being easily attained in 15 minutes of cooling, and the accuracy of maintenance of the mean renal core temperature is shown in Figure 5. Using this polystyrene insulated system, the renal temperatures could be

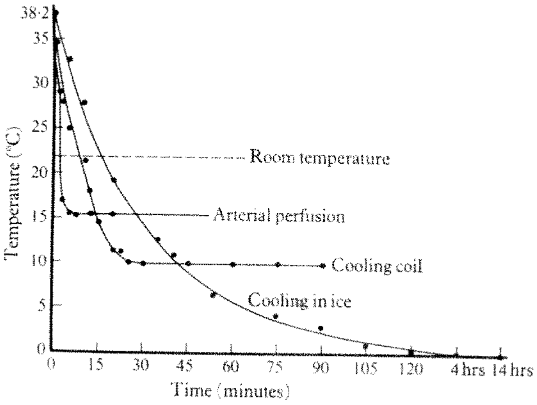


Fig. 4. Kidney cooling by immersion in ice, cooling coil, and arterial perfusion.

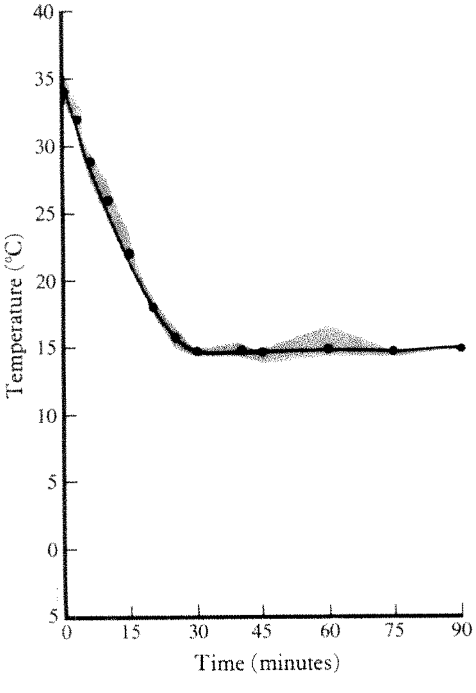
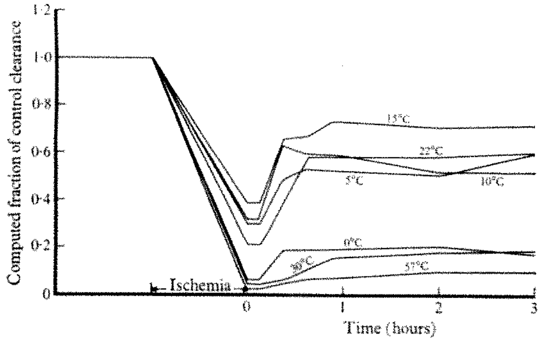


Fig. 5. Regional renal hypothermia cooling to 15°C.

maintained accurately within 1° to 2°C. The renal temperatures of all 5 test animals fell within the shaded areas on the graph.

The results of GFR and TmPAH in relation to time and temperature group were entered on computer cards and the computer was programmed to calculate all the post-ischaemic function ratios in relation to the mean of their own 3 control values. It then calculated mean function values for each group of 5 dogs in relation to time. A visual comparison of each group of 5 dogs was made by plotting the computed mean fraction of function against time and temperature for both GFR and TmPAH and thus the optimum temperature was exposed (Figs 6 to 9). A computer statistical analysis was performed.



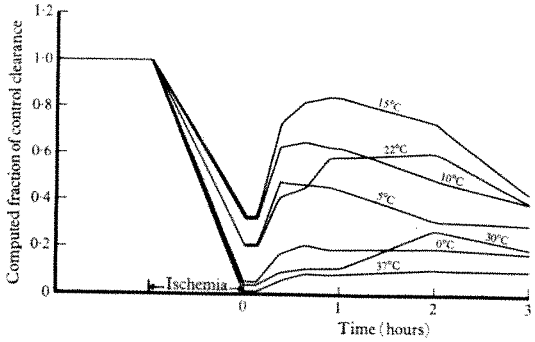
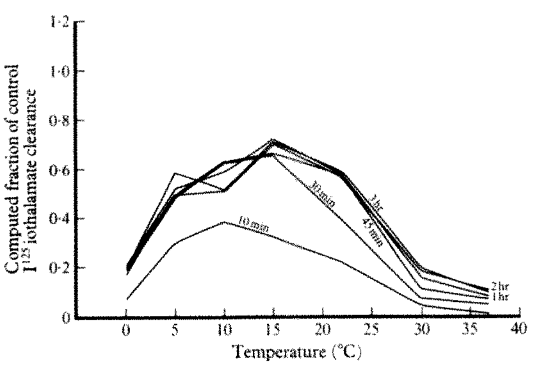


Fig. 6. ^{125}I iothalamate clearance in the canine kidney. 90 minutes ischaemia at various temperatures.

Fig. 7. TmPAH in the canine kidney. 90 minutes ischaemia at various temperatures.



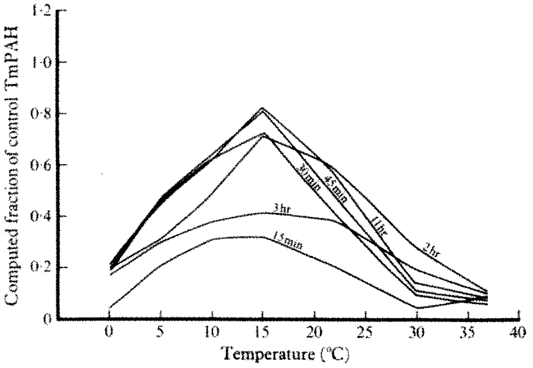


Fig. 8. ^{125}I iothalamate clearance in the canine kidney following 90 minutes ischaemia at various temperatures.

Fig. 9. TmPAH in the canine left kidney. following 90 minutes ischaemia at various temperatures

Discussion and Conclusions

15°C has been shown to be the optimum temperature for protecting the canine kidney during 90 minutes of experimental renal ischaemia. This temperature afforded optimum protection to glomerular and tubular function as measured by ^{125}I sodium iothalamate ($P = 0{\cdot}0001$) and TmPAH ($P = 0{\cdot}0093$). Temperatures either higher, 37°, 30° and 22°C, or lower, 10°, 5° and 0°C, afford less protection with subsequent decreased function. The considerable functional loss caused by ischaemia at 5° and 0°C is at variance with Stueber *et al.* and Fegen *et al.* Whether the

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reduction of function is induced by the direct effect of hypothermia on the renal cells or by alterations in intrarenal nutrient blood flow, the potential of injury to the cells is still present. Renal blood flow studies together with another method of assessing kidney damage would therefore be extremely useful in elucidating this question, hence the enzyme release studies.

Further Studies

Measurements of total renal blood flow showed no significant change following the ischaemic period and renal arteriograms both *in vivo* and extracorporeal (Fig. 10) were unhelpful in measuring changes in intrarenal blood distribution. Isotope labelled platelets suggested that renal functional depression following ischaemia may in part be due to alterations of intrarenal effective nutrient blood flow and that platelet aggregation was not a factor in this mechanism. Histological studies, plasma lactic dehydrogenase, its isozymes and plasma γ-glutamyl transpeptidase (γ-GT) were found to be of limited value in the measurement of ischaemia injury (Ward, 1973).

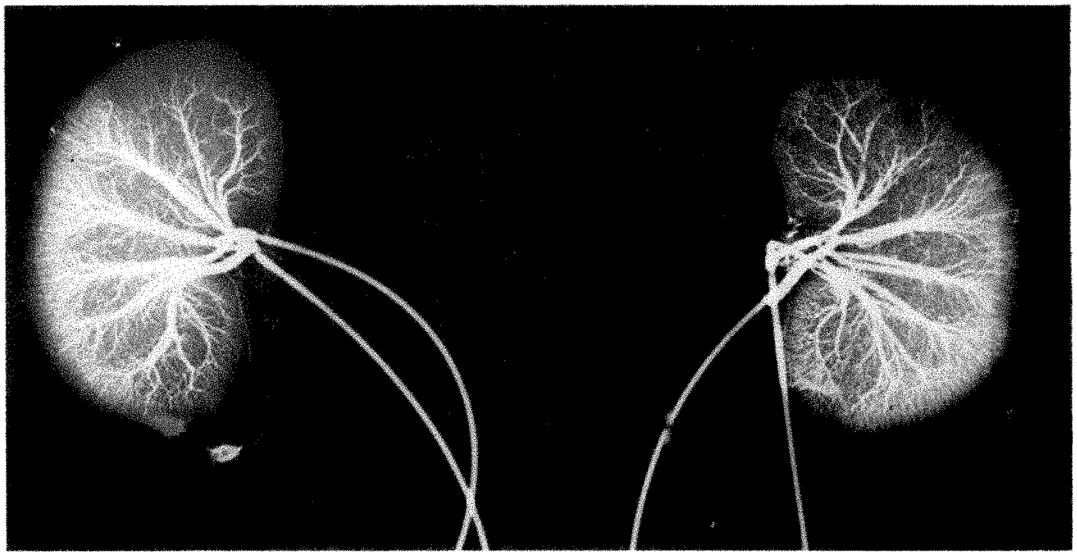

Fig. 10. Bilateral extracorporeal canine renal arteriograms using Micropaque. The kidney having undergone 90 minutes ischaemia at 15°C is shown on the right. The contralateral kidney is shown as a control.

Gamma glutamyl transpeptidase is an enzyme primarily located in the brush border of the proximal convoluted tubule of the kidney (Glenner, Folk and McMillan, 1962). The urinary activity of γ-glutamyl transpeptidase has been shown to be increased following renal artery clamping, and provides a sensitive measure of renal ischaemic injury. The urinary γ-GT was therefore measured in the 3 hours following the ischaemia in all 5 dogs of each temperature group, using the kinetic photometric method described by Szasz (1969), a simple one-step colour reaction requiring no incubation.

The normal urinary excretion of γ-GT from a single kidney in the dog is 348 to 1,303m Units in 3 hours. The 3 hour urinary γ-GT following 90 minutes ischaemia at 37°, 30°, 22°, 15°, 10°, 5° and 0°C is shown in Figure 11.

Urinary γ-GT activity was significantly reduced following ischaemia at 15°C compared with the higher values obtained at 22°, 30° and 37°C ($P = 0{\cdot}016$), being additional evidence that 15°C is the optimum temperature. Cooling the kidney below 15°C produced no significant additional protection to ischaemia as measured by urinary γ-GT activity.

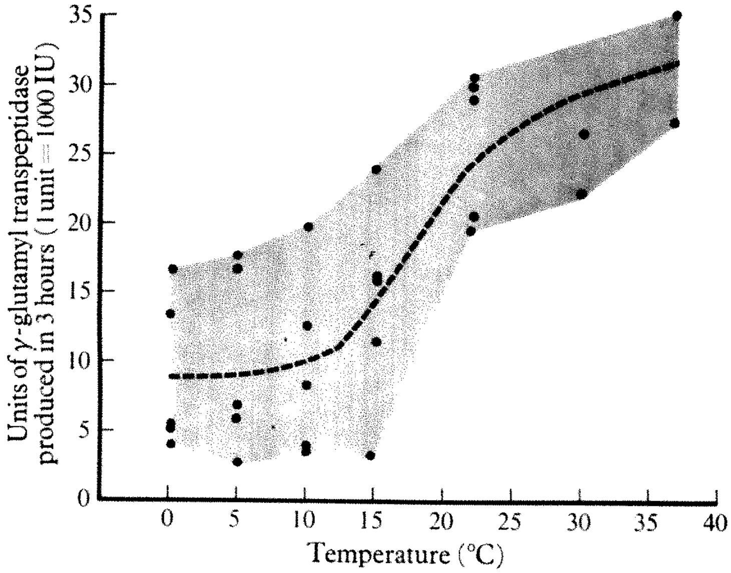

Fig. 11. γ-Glutamyl transpeptidase activity in canine urine following 90 minutes complete renal ischaemia at various temperatures.

Conclusions

The evidence from these studies of hypothermia in experimental canine renal ischaemia is sufficiently significant to warrant its application to surgical renal ischaemia in man. The hypothesis that an optimum temperature for regional hypothermia in renal ischaemia exists is confirmed and is localised at 15°C.

Summary

To determine the optimum temperature at which the *in situ* kidney should be maintained while it is ischaemic, 47 mongrel dogs were studied.

35 of these underwent 90 minutes of left renal ischaemia with the kidney temperature maintained at 37°, 30°, 22°, 15°, 10°, 5° and 0°C respectively.

The effect on renal function was determined by measurements of G.F.R. before and at regular 15-minute intervals after the ischaemic period. Computer statistical analysis exposed the optimum temperature to be 15°C.

Renal artery blood flow, renal histology, ^{51}Cr labelled platelets and renal arteriography were used to determine the mechanism of ischaemic injury.

Quantitation of renal cell injury confirmed that no additional protection to ischaemia could be gained by cooling below 15°C.

15°C is recommended as the optimum temperature for use in clinical renal hypothermia.

My thanks to Professor B. Eiseman, the Department of Surgery, University of Colorado Medical Centre, Denver, USA, Mr J. E. A. Wickham, the J. Hartford Foundation, Grant No. 66097, and N. I. H. Grants GM. 20309, AM 17022 and HL 15873, and the Wellcome Trust.

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Conservative Renal Surgery for Adenocarcinoma. The Place of Bench Surgery

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Radical surgery is impossible when renal adenocarcinoma occurs either in the solitary kidney or simultaneously in both kidneys.

How, therefore, can patients in these two situations best be helped and what is the likely outcome of conservative surgical treatment of their tumours? It is proposed to examine this problem in the following ways: by a brief review of the literature, by a report of cases personally treated, by a description of the operative technique used and, finally, by a discussion on the advantages and disadvantages of *ex vivo* bench surgery.

I. Review of the Literature

A search of the English literature has been made to find: (i) reports of cases of tumour occurring in a solitary kidney; and (ii) reports of cases which have initially presented as bilateral lesions.

In any retrospective series it is difficult to draw completely valid conclusions about effectiveness of treatment due to lack of comparable histological and survival detail but nevertheless several general trends have emerged.

(i) *Tumours in a Solitary Kidney*

Including the cases reported in this paper, 51 patients with tumours occurring in solitary kidneys are available for study (Table I).

These cases may be considered in 2 groups depending upon the nature of the lesion determining the loss or absence of the contralateral kidney.

Group 1 *Malignant. Where the contralateral kidney was removed for an antecedent adenocarcinoma—27 cases.*

Survival 10 (37%) were alive (mean survival 26 months)
15 (55%) were dead (mean survival 23 months)
2 (8%) were lost to follow-up.

Group 2 *Benign. Where the other kidney was either agenetic or had been removed for a benign condition—25 cases.*

Survival 17 (68%) were alive (mean survival 30 months)
6 (24%) were dead (mean survival 8 months)
2 (8%) were lost to follow-up.

Conclusion

There is thus a very striking difference between the survival of patients with a benign as opposed to a malignant contralateral lesion.

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

Table I

Tumours in Solitary Kidneys

Author	Reference Year	Data on Other Kidney	Treatment	Survival after Diagnosis of Tumour in Solitary Kidney
1 Beilin	1942	Carcinoma 6 years before	None	Dead—30 months
2 Senger	1947	Carcinoma 2 years	Deep X-ray	Dead—36 months
3 Bailey	1950	Carcinoma 11 years	None	Dead—30 months
4 Borski	1954	Carcinoma 3 years	Deep X-ray	Dead—30 months
5 Semb	1954	TB, ? time	Partial nephrectomy	Not known
6 Colston	1955	Agenesis	Partial nephrectomy	Dead—5 months
7 Svab	1956	Agenesis	Partial nephrectomy	Alive—12 months
8 Kerr	1959	Agenesis	Partial nephrectomy	Alive—4 months
9 Meyer	1960	Carcinoma 2 years	Chemotherapy	Dead—9 months
10 Klotz	1960	Carcinoma 20 years	Partial nephrectomy	Alive—12 months
11 Smith	1961	Dysplasia	Partial nephrectomy	Alive—16 months
12 Andre	1962	Pyelonephritis 11 years	...	Alive—120 months
13 Ballanger	1962	Agenesis	Partial nephrectomy	Alive—15 months
14 Ewert	1962	Agenesis	Partial nephrectomy	Not Known
15 Flemming	1964	Agenesis	Partial nephrectomy	Alive—24 months
16 Dick	1964	Atrophic	Partial nephrectomy	Alive—5 months
17 Rolnick	1965	Agenesis	Partial nephrectomy	Dead—5 months
18 Malament	1965	Carcinoma 4 years	Deep X-ray	Dead—168 months
19 Gray	1967	Agenesis	Partial nephrectomy	Alive—60 months
20 Bloom	1967	TB	Hormones	Dead—3 months
21 McDonald	1967	Pyonephrosis	Partial nephrectomy	Alive—60 months
22 Zinman	1967	Agenesis	Partial nephrectomy	Alive—60 months
23 Zinman	1967	Hypoplasia	Partial nephrectomy	Alive—36 months
24 Zinman	1967	Kidney used for portal vein surgery	Partial nephrectomy	Alive—18 months
25 Kaufman	1968	Agenesis	Deep X-ray	Dead—18 months
26 Kaufman	1968	Agenesis	Partial nephrectomy	Dead—1 month
27 Kaufman	1968	Carcinoma 4 years	Partial nephrectomy	Alive—30 months
28 Kaufman	1968	Carcinoma 8 years	Partial nephrectomy (Testosterone)	Dead—6 months
29 Kaufman	1968	Carcinoma 8 years	Deep X-ray (Testosterone)	Dead—6 months
30 Kaufman	1968	Agenesis	Partial nephrectomy	Alive—9 months
31 Parker	1969	Hydronephrosis	Radical nephrectomy	Well on dialysis—24 months
32 Parker	1969	Atrophic pyelonephritis	Partial nephrectomy	Alive—37 months
33 Parker	1969	Carcinoma 3 years	Chemotherapy (Actinomycin)	Dead—9 months
34 Parker	1969	Infection	Partial nephrectomy	Dead—12 months
35 Parker	1969	Carcinoma 10 years	Deep X-ray	Alive—45 months
36 Parker	1969	Hydronephrosis	Partial nephrectomy and Deep X-ray	Dead—8 months
37 Parker	1969	Carcinoma 25 years	None	Alive—31 months
38 Parker	1969	Carcinoma 16 years	Deep X-ray (Testosterone)	Alive—6 months
39 Calne	1971	Carcinoma	Partial nephrectomy, auto-transplant	Alive—28 months
40 Vermillion	1972	Carcinoma 18 years	None	Died—1 month
41 Vermillion	1972	Carcinoma 3 years	None	Died—6 months
42 Vermillion	1972	Carcinoma 9 years	None	Lost to follow up
43 Vermillion	1972	Carcinoma 2 years	Partial nephrectomy	Died—1 month
44 Vermillion	1972	Carcinoma 15 years	Deep X-ray	Died—12 months
45 Vermillion	1972	Carcinoma 3 years	Partial nephrectomy	Died—8 months
46 Vermillion	1972	Carcinoma 12 years	None	Died—1 month
47 Vermillion	1972	Carcinoma 13 years	None	Lost to follow up
48 Vermillion	1972	Carcinoma 10 years	Partial nephrectomy	Alive—32 months
49 Wickham	1974	Carcinoma 5 years	Partial nephrectomy	Alive—57 months
50 Wickham	1974	TB 7 years	Partial nephrectomy	Dead—3 months
51 Wickham	1974	Carcinoma 14 years	Partial nephrectomy	Alive—6 months

Type of Treatment of the 48 cases followed up:

Partial Nephrectomy. 28 cases were treated by conservative partial nephrectomy.
Of these 28 patients so treated, 72% were alive (mean follow up 31 months).
28% were dead (mean follow up 5 months).

Other Treatments. 20 patients were either not treated or had deep X-ray therapy with or without hormones or chemotherapy.
25% were alive (mean follow up 24 months)
75% were dead (mean follow up 24 months)

Conclusion

Assuming a random scatter of histological differentiation and tumour progression in both groups partial nephrectomy would appear to be the treatment of choice for this type of lesion.

(ii) *Tumours presenting Bilaterally and Simultaneously*

25 cases are available for study, including one reported in this paper (Table II). Of these cases:

(a) *Survival*

18 patients (72%) were dead within 6 months of presentation.
5 patients (20%) were alive at 21 months mean follow-up.
2 patients (8%) lost to follow-up.

(b) *Treatment*

In 7 cases where the tumours were treated aggressively by total nephrectomy on one side and partial nephrectomy on the other, or by bilateral partial nephrectomy:

5 patients (70%) were alive at 23 months mean follow-up.
2 patients (30%) were dead mean follow-up 12 months.

In 16 patients where no treatment, non-radical surgery, deep X-ray therapy or chemotherapy was offered, all were dead within 5 months. (100%)

Conclusion

The simultaneous appearance of tumours in both kidneys is an ominous sign, indicating a very poor prognosis. It seems that an aggressive surgical attack on both kidneys offers a very much better chance of survival than any other form of treatment.

Is the contralateral tumour a metastasis or a new primary tumour?

Two situations are possible, either the patient has developed bilateral primary tumours or the contralateral kidney is involved in a metastatic spread from a primary tumour on the other side.

Looking first at the "*malignant*" group of solitary tumours, there is a considerable variation in time between presentation of the first lesion and the appearance of the second, the range being from 25 years down to 2 years.

If, in those patients who have been treated by partial nephrectomy, the time of presentation between the two tumours is compared to the length of survival, it is interesting to find that patients who died of this disease had a mean interval between tumour incidence of 6 years whilst those who lived had a mean incidence exactly double at 12 years.

Assuming a metastatic contralateral spread, this difference could possibly be accounted for on the basis that those who died with a shorter incidence interval had more aggressive metastasising tumours and also that the simultaneous presenters had the most aggressive tumours of all being metastatic from one side to the other, a fact confirmed by their poor survival and evidence of widespread dissemination of their tumours at death (Bastable, 1960).

Table II

Bilateral Tumours

	Author	Year	Right	Left	Treatment	Results
1	Chute	1910	Upper pole	All kidney	Laparotomy	Dead—1 month
2	Weber	1915	All kidney	All kidney	None	Dead—1 month
3	Hunt	1927	3 cm tumour	All kidney	L. nephrectomy	Dead—1 month
4	Kinsey	1927	Multiple tumour	Multiple tumour	None	Not known
5	Sanford	1931	Multiple tumours	Multiple tumours	R. nephrectomy	Dead—1 month
6	Sprenger	1935	Local tumour	Large mass	None	Dead—< 1 month
7	Sprenger	1935	Mid kidney	Lower pole	None	Dead—< 1 month
8	Jeck	1936	5 cm tumour	Large mass	L. nephrectomy	Dead—1 month
9	Hortolomei	1937	Multiple	Multiple	None	Not known
10	Elward	1940	Large mass	Large mass	None	Dead—10 months
11	Forsythe	1942	Large tumour	Small tumour 6 cm	R. nephrectomy	Dead—< 1 month
12	Hanley	1945	Large mass	Upper pole	None	Dead—10 months
13	Alnor	1952	Lower pole	Upper pole	R. nephrectomy	Dead—1 month
14	Rumelhardt	1953	Lower pole	Upper pole	None	Dead—1 month
15	Thompson	1958	Large mass	Large mass	None	Dead—< 1 month
16	Krumbach	1959	Upper pole	Generalised	L. nephrectomy R. partial nephrectomy	Alive—60 months
17	Bastable	1960	Upper pole	Lower pole	Laparotomy	Dead—3 months
18	Small	1967	Small tumour	Small tumour	R. nephrectomy L. partial nephrectomy	Alive—12 months
19	Kölln	1971	Small tumour	Small tumour	Bilateral partial nephrectomy (2)	Alive—27 months
20	Vermillion	1972	Small tumour	Small tumour	R. nephrectomy L. partial nephrectomy	Died—6 months
21	Vermillion	1972	Upper pole	Left small tumour	R. nephrectomy	Died—1 month
22	Vermillion	1972	Upper pole	Left lower pole	L. nephrectomy R. intra-arterial perfusion	Died—48 months
23	Calne	1973	Mid zone	Lower pole	Bilateral partial nephrectomy auto-transplant	Alive—14 months
24	Calne	1973	Lower pole	Lower pole	Bilateral partial nephrectomy auto-transplant	Alive—4 months
25	Wickham	1974	Upper pole	Lower pole	Bilateral partial nephrectomy	Dead—18 months

It would therefore seem that all these tumours, both solitary and bilateral, could constitute part of one disease spectrum and that the time of presentation of the contralateral and possibly metastatic lesion is determined purely by the aggressiveness of their primary tumour.

If, on the other hand, the development of the contralateral tumour was in the nature of a second primary, one would expect survival rates in the malignant group to be comparable to those of the benign group. This, as has been shown above, is clearly not so, patients in the "*benign*" group surviving nearly twice as well as in the "*malignant*" group. Finally, if both kidneys are equally susceptible to carcinogenic influences one might expect a considerably higher incidence of simultaneous bilaterally occurring primary tumours, but this is a very rare event.

Conclusion

Where one kidney has been removed for adenocarcinoma the appearance of tumour on the other side seems more likely to be due to the progression of a metastatic lesion, rather than to the development of a new primary tumour. The rate of progression of the second lesion is determined by the degree of aggressiveness of the primary, the simultaneous bilaterally appearing tumours being evidence of a rapidly progressive high grade lesion.

Implications

1. Apart from the obviously increased operative risk, the prognosis for a patient with a tumour appearing in a solitary kidney where the other organ has been lost for a benign condition would seem no worse than that for a patient developing a tumour in one of a pair of normal kidneys.
2. When a patient develops a tumour in a solitary kidney when the other kidney has been removed for adenocarcinoma, the prognosis is only half as good as for a primary lesion and the prognosis worsens with shortening of the incident interval.
3. Bilateral simultaneous tumours have a bad prognosis and are high-grade metastasising lesions.
4. Aggressive conservative surgery for both types of lesion carries the best chance of survival.
5. Should we be doing conservative resection of well differentiated tumours? Our experience to some extent confirms these conclusions.

II. Case Reports

Case 1. K. L., aged 56 years. 28.11.69—Prostatism; IVP bilateral space occupying (SOL) lesion of kidneys, confirmed by angiography (Fig. 1, A and B). 9.12.69—Right upper polar resection of tumour under hypothermia; 56 min ischaemia (discharged 10 days). 2.3.70—Left lower polar resection of tumour under hypothermia; 59 min ischaemia (discharged 14 days). Postoperative progress satisfactory. Histology: identical poorly differentiated adenocarcinomas. Survival: 13 months—death from multiple metastases.

Case 2. J. K., aged 49 years. 16.1.64—Haematuria; IVP, SOL right kidney. 20.1.64—Right nephrectomy. 20.1.69—Pain in left side; IVP, SOL left kidney confirmed on angiography (Fig. 2). 6.3.69—Lower polar tumour resected under hypothermia; 50 min ischaemia (discharged 14 days). Histology: moderately differentiated adenocarcinoma. Survival: alive and well 57 months.

Case 3. A. C., aged 51 years. 1964—Left nephrectomy for tuberculosis. 12.1.71—Haematuria; IVP, SOL right kidney, confirmed on angiography (Fig. 3). 6.6.71—Right upper polar resection; glands involved by tumour; 40 min ischaemia, but profound fall in central BP; no arterial flow on declamping—patch graft to artery—total ischaemia 4 hr. Postoperative recovery following dialysis—4 weeks. Histology: poorly differentiated adenocarcinoma. Survival: 3 months, death from multiple metastases.

Case 4. C. M., aged 54 years. 28.1.60—Mass in right loin; IVP, SOL right kidney. 1.2.60—Right nephrectomy. 23.2.65—Solitary pulmonary metastasis resected. 8.1.74—Haematuria followed by anuria; IVP showed obstructed left kidney with SOL confirmed by angiography (Fig. 4). 11.1.74—Resection of lower polar tumour under hypothermia; ischaemia time 60 min (discharged 10 days). Histology: Moderately differentiated adenocarcinoma comparable to initial tumour. Survival: 6 months—alive and well.

III. Technical Methods of Treatment for this type of Lesion

Two principal methods of treatment are available:

1. Partial nephrectomy *in situ*.
2. Partial nephrectomy *ex vivo*—so-called "Bench Surgery".

1. Partial Nephrectomy

By the nature of the disease and its random spread through the kidney a standard partial nephrectomy of the tumour with ligation of individual segmental vessels is seldom possible.

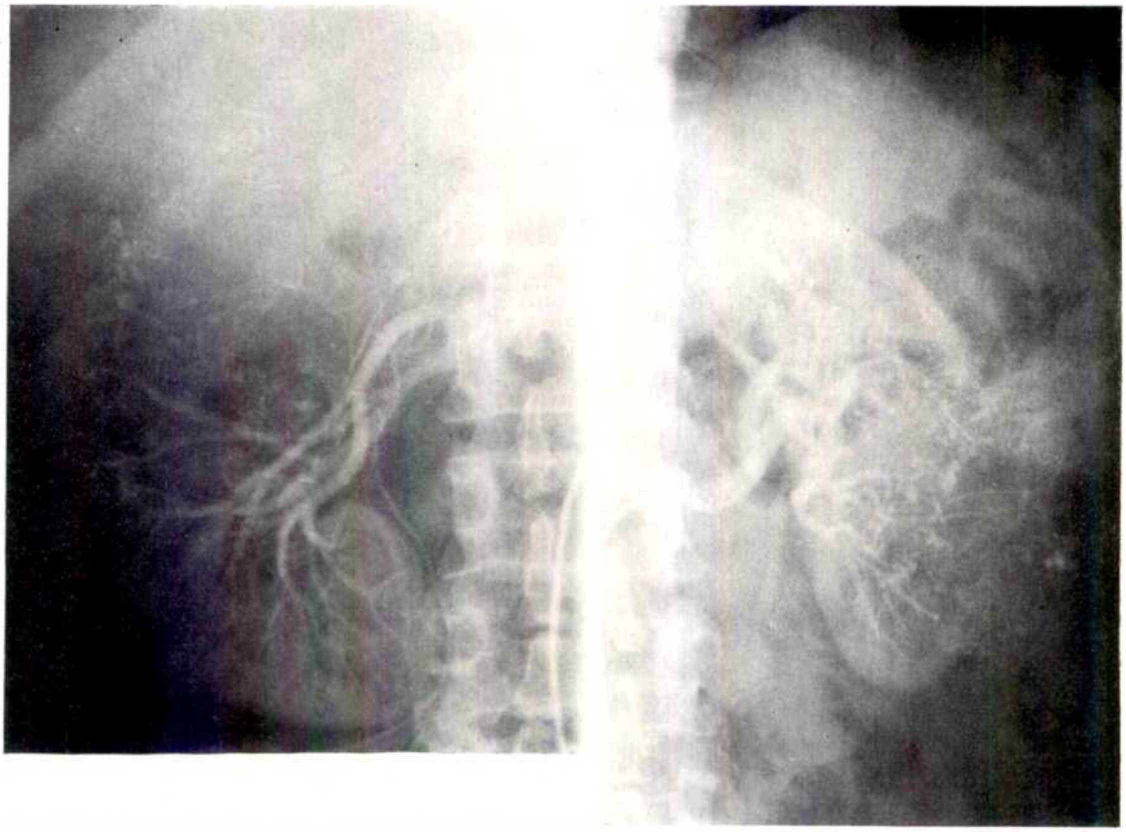


Fig. 1 A and **B**, Bilateral space-occupying lesion of kidneys confirmed by angiography.

Frequently the tumour extends across several segmental vascular territories and the only method of removal is a careful excision of the tumour-bearing area with a sufficient margin of normal renal tissue under direct vision. For accuracy it would seem essential that this procedure should be carried out in dry field with vascular arrest. With a small peripheral tumour it is possible to perform excision quite quickly but for central or multiple lesions some form of regional hypothermia is indicated to preserve function during prolonged ischaemia and this method has been used in the cases reported above.

The Operation

The kidney is gently mobilised, the artery and vein are exposed and the artery occluded with a small bulldog clamp. Heat exchanger coils are applied (Fig. 5, A and B) and the kidney cooled to 15° to 20°C with cold water from an external electric refrigerator (Fig. 6). Careful local dissection of the tumour is then undertaken in a dry field (Figs. 7 and 8). The kidney may be stabilised with a "net-elast" sling if desired and magnifying spectacles can help with visualisation. The margins of the tumour are visualised easily and subsequent histological examination has confirmed the completeness of the excision. It may be necessary to occlude the renal vein when the tumour involves the hilar area, as free venous reflux can occur from the cava and obscure the operative field.

Finally, the collecting system is reconstructed (Fig. 9) and haemostasis achieved by oversewing

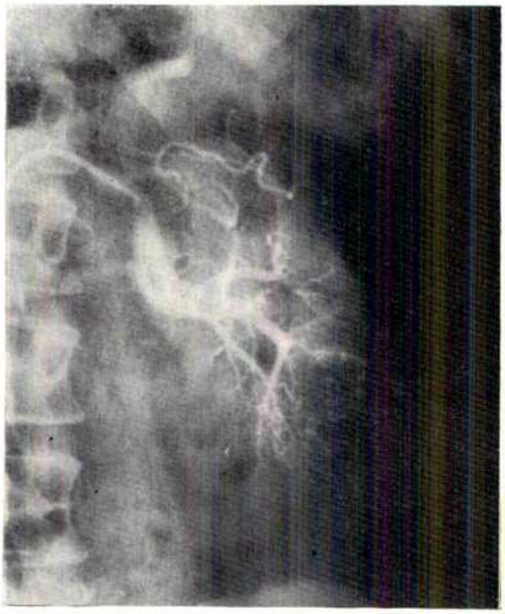


Fig. 2. Angiogram showing tumour of lower pole.

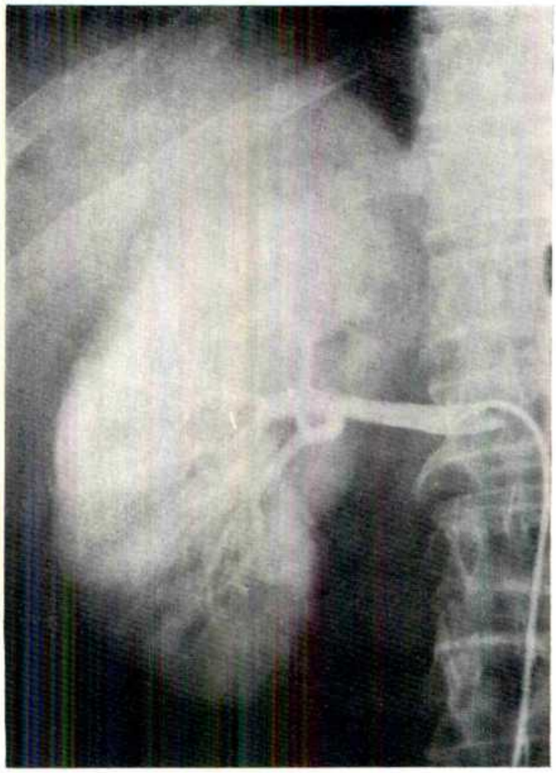


Fig. 3. Tumour of upper pole.

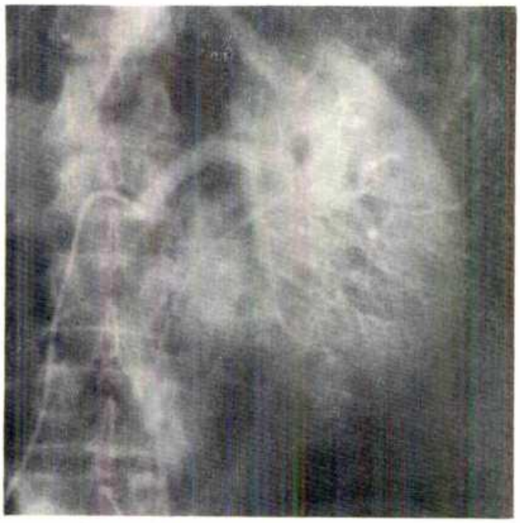


Fig. 4. Angiogram showing tumour of lower pole, left kidney.

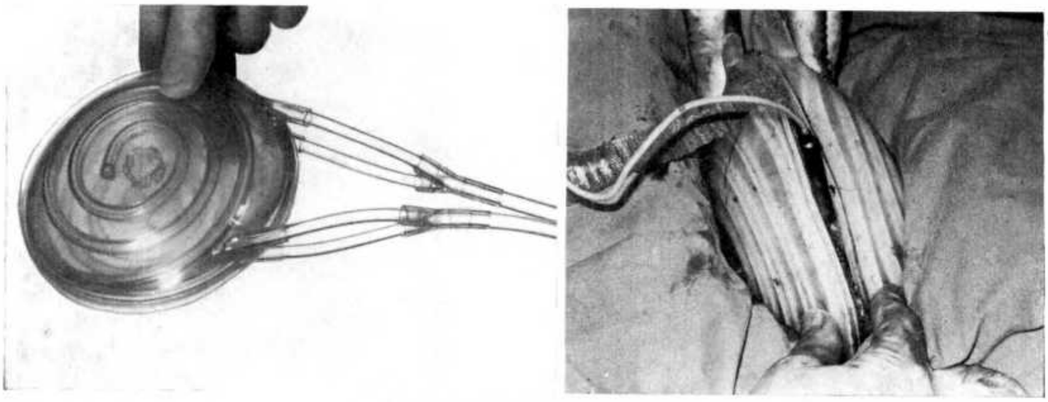


Fig. 5. **A** and **B**, Heat exchange coils.

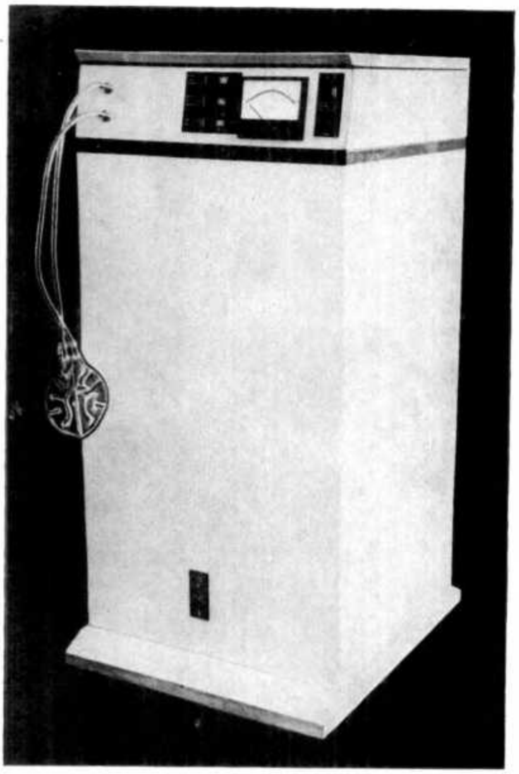
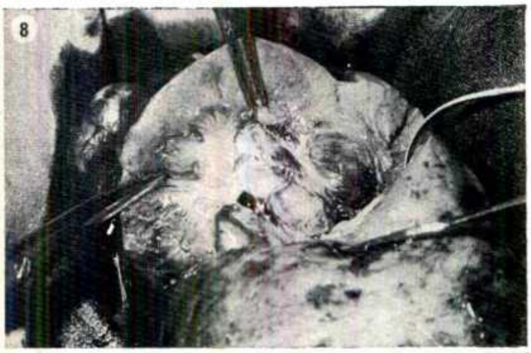


Fig. 6. External electric refrigeration.

and ligation of vessels. A 12 F nephrostomy tube is inserted (Fig. 10) to obviate clot colic and the wound closed routinely.

Apart from the one occasion requiring dialysis after prolonged ischaemia, the patients left hospital within 14 days of each procedure.



Figs. 7 and 8. The various stages of dissection of the tumour.

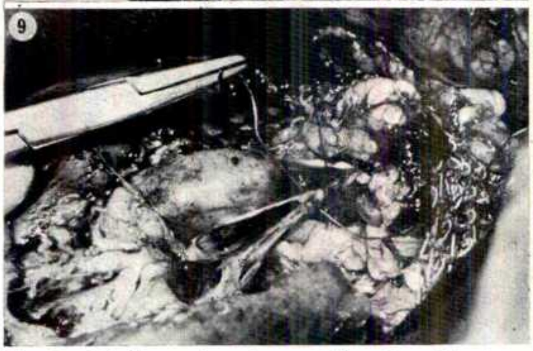


Fig. 9. The collecting system being reconstructed.

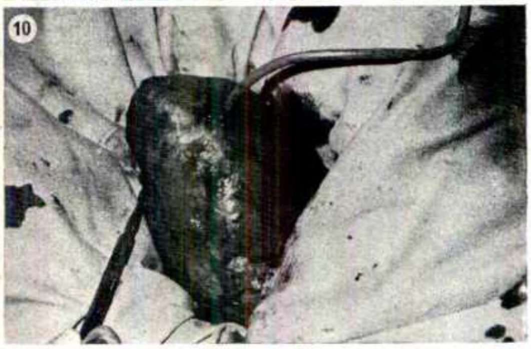


Fig. 10. Nephrostomy tube inserted.

2. Ex vivo *Partial Nephrectomy*

Excision of the kidney, *ex vivo* correction of a pathological lesion and autotransplantation of the organ to the iliac fossa is currently fashionable.

The method was first described by Hardy (1963) and was used to overcome a high ureteric injury. Since then the technique has been used by many workers for the correction of renal artery anomalies and more recently for the excision of tumours in solitary kidneys.

Once the kidney has been removed renal function must be supported by either:

(1) hypothermic infusion of an intracellular type of electrolyte solution such as Sachs or Collins media, or

(2) the organ must be maintained on continuous mechanical perfusion with a hypothermic protein containing perfusate.

When the preservation procedure is under way, the renal tumour is again excised in a manner similar to that described above.

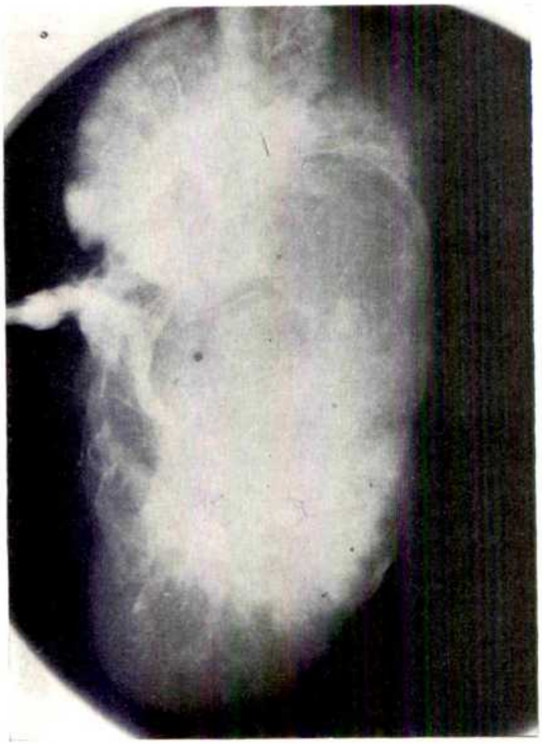
The organ is finally re-implanted into the iliac fossa as in renal transplantation. The ureter may or may not be detached from the bladder during the *ex vivo* procedure.

IV. Discussion on the Advantages and Disadvantages of *ex vivo* Partial Nephrectomy

Advantages

1. The principal advantage claimed is that of visualisation and accessibility. It is hard to see, however, what greater degree of accessibility to the kidney could be desired than that found in the *in situ* situation compared with accessibility to the bench kidney.

2. The second advantage claimed is that it is possible to perform angiography on the dissected organ and that such pictures provide guidance to adequate excision of the tumour.



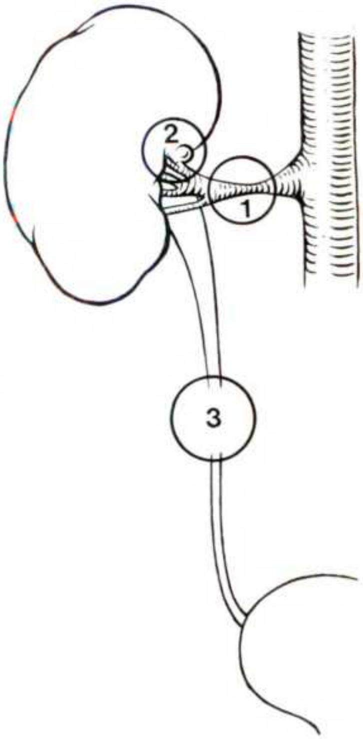


Fig. 11. Bench angiogram showing central tumour with vascular supply.

Fig. 12. Indications for "Bench Surgery". (1) Vascular conditions involving the whole renal artery. (2) Detailed surgery on peripheral arteries. (3) Bridging of large ureteric defects.

This type of angiogram is shown in Figure 11, where a kidney containing a central tumour was perfused on the Gambro machine and hypaque 45% injected, intra-arterially. It is obvious that the tumour is supplied from several segmental areas, that angiography is not very helpful in delineating the tumour and that ligation of individual small vessels would be impossibly time-consuming and counter-productive. In contrast, simple section of the kidney with secondary haemostasis has been found to be a very satisfactory manoeuvre.

3. The possibility of the injection of cytotoxic drugs into the isolated kidney has been suggested but does not appear to have been used clinically.

The Disadvantages

1. The increased complexity of the technique; cannulation of vessels is required and special perfusates are a necessity.

2. Increased patient morbidity. Auto-transplantation extends the operation time to the order of 4 to 5 hours. The patient is subjected to a second incision, or generous extension of the primary incision.

3. The added complications that may arise from the vascular anastomoses cannot be excluded together with problems of ureteric implantation, leakage, fistula and infection which have been described after this procedure.

4. Reports of permanent non-function of the kidney following the procedure are recorded when it has been used for the correction of vascular anomalies (Hodges *et al.*, 1973).

5. Time in hospital: Patients undergoing *in situ* partial nephrectomy generally leave hospital within 14 days—compare this with the time spent after auto-transplantation (Calne, 1973—one month, 2 months and 4 months).

Conclusion

It would seem that treatment of the tumour in a solitary kidney or bilateral renal adenocarcinoma should be by *in situ* partial nephrectomy under hypothermia, a simple well tried and effective procedure.

An *ex vivo* technique for this condition although superficially attractive has no advantages, many disadvantages and unnecessarily complicates a simple situation.

The primary indications for "Bench Surgery" would seem to be (Fig. 12):

1. The correction of vascular conditions involving the whole length of the main renal artery.
2. Detailed surgery on peripheral arteries requiring magnification.
3. The bridging of large upper ureteric defects without the involvement of a bowel replacement segment.

Partial nephrectomy is part of the everyday urological repertoire and is a simple and satisfactory method of treatment for tumours of this type.

Summary

A brief review of reported cases of tumours in solitary kidneys and of bilateral simultaneously occurring tumours is reported.

1 case of bilateral simultaneously occurring tumour and 3 cases of tumour occurring in solitary kidneys are reported.

The treatment of these cases by simple partial nephrectomy under regional hypothermia is described.

The place of *ex vivo* "Bench Surgery" for this condition is discussed.

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Continuous Perfusion of Human Cadaveric Kidneys for Transplantation

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Good HLA matching in renal cadaveric transplantation significantly improves the transplant survival rate (Dausset and Hors, 1972; Oliver *et al.*, 1972) but this can be achieved only by transportation of kidneys between different units resulting in an increase in cold ischaemia time. Furthermore, it is desirable to perform transplantation as an elective procedure provided that ischaemic damage can be halted by good preservation methods. Simple storage methods have given satisfactory results provided the total ischaemia time does not exceed 10 hours (Hulme *et al.*, 1972). More recently, however, it has been shown that if the cold ischaemia time is over 7½ hours primary failure rate is increased to 41% and to 59% if over 9 hours (Hall *et al.*, 1974).

Preliminary studies with canine kidneys using the Gambro perfusion machine showed that satisfactory preservation could be achieved for up to 96 hours without warm ischaemia, or up to 48 hours with 1 hour's warm ischaemia (Claes and Blohmé, 1973). Good results have been reported with 240 cadaveric kidneys stored for up to 40 hours (Blohmé and Claes, 1973). After studying this technique at the transplantation unit in Gothenburg, this preservation method was introduced in the London Transplant group in June 1972, and the results of 63 human cadaveric kidneys are reported.

Materials and Methods

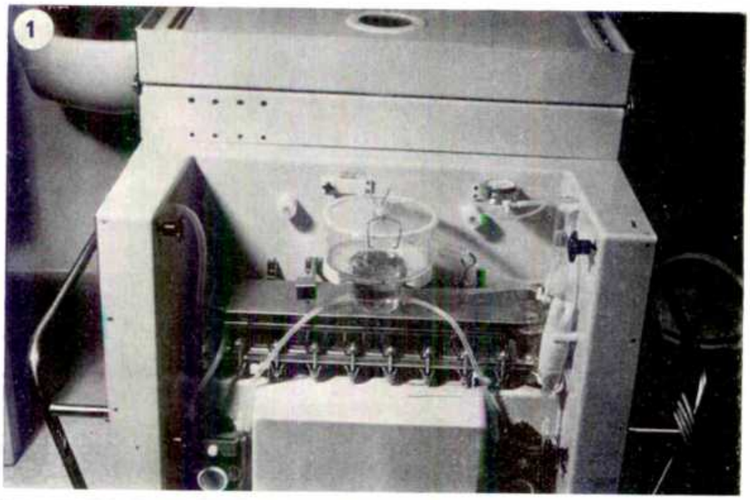
The machine consists of a disposable perfusion circuit housed in an insulating cabinet which contains the controls, batteries, motors and gas cylinder (Fig. 1).

Iced water is circulated through a heat exchanger under thermostatic control and this maintains the temperature at about 5°C. Perfusate is pumped at a constant rate through the heat exchanger and membrane oxygenator which is gassed with 66% nitrogen, 33% oxygen and 1% carbon dioxide mixture. In a second circuit perfusate is pumped through a leucocyte filter and bubble trap to the kidney. The flow is adjusted to give a perfusion pressure of 60 mm of mercury systolic, and flow rate is measured by timing the speed of the roller pump. The temperature is checked by a small thermometer in the organ chamber beside the kidney (Fig. 2).

The perfusate medium consists of human serum albumin 20% (Kabi) 200 ml, saline solution (0·9 g/100 ml) 500 ml, glucose solution (5·5 g/100 ml) 100 ml, soluble insulin 80 units, magnesium sulphate 10 mEq, potassium chloride 4 mEq, papaverine HCl 40 mg, benzylpenicillin 1 million units, hydrocortisone 100 mg, and sodium bicarbonate about 20 mEq (to adjust pH to 7·0-7·2).

63 consecutive human cadaveric kidneys passing through the London Transplant group were preserved between June 1972 and October 1973. Donors were aged between 7 and 70 years. Initial warm ischaemia varied between 5 and 60 minutes. All kidneys received had been flushed with perfudex, Gelin's solution (Brunius, Fritjofsson and Gelin, 1967) or Collins intracellular medium (Collins, Bravo-Shugarman and Terasaki, 1969). Most kidneys would have been regarded as acceptable for transplantation by criteria used before the introduction of this preservation method but latterly some kidneys of doubtful viability were "assessed" on perfusion (for example, from failed open heart surgery, and kidneys which had not been flushed initially).

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.



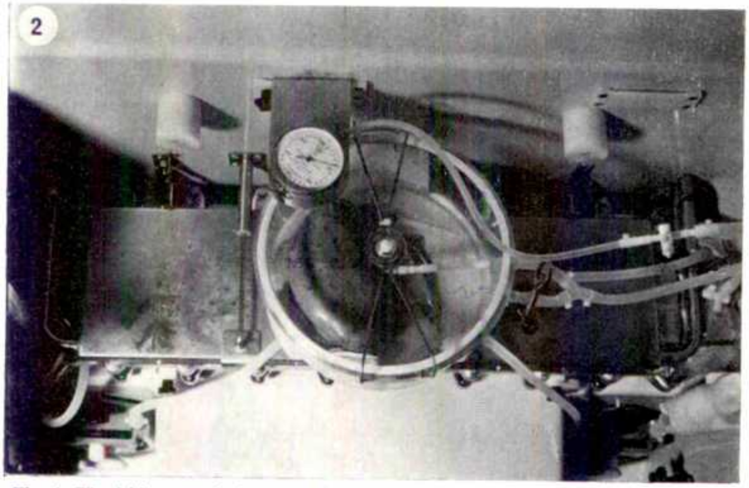


Fig. 1. The kidney perfusion machine during renal preservation.
Fig. 2. The kidney perfusion machine (Gambro) with the disposable unit primed.

Kidneys were preserved in ice slush for 0 to 12½ hours during transport to the machine and were then perfused for 2½ to 28 hours in the laboratory. On 44 occasions the machine was transported to the recipient hospital (on two occasions the kidneys were transferred to the machine of the recipient hospital) (Fig. 3). 8 kidneys were removed from the machine and transported to the recipient in ice with a post-perfusion cold ischaemia of 1 to 10 hours. 11 kidneys with perfusion flow rate of less than 100 ml/min were discarded, following the recommendations established at the kidney transplantation unit in Gothenburg.

Results

63 kidneys were perfused and 52 were transplanted: 13 (25%) functioned immediately, 23 (44%) functioned after a delay of 2 to 28 days, and 16 (31%) failed to function at all; 11 kidneys with poor perfusion flow were discarded. Of kidneys followed for more than 6 months after transplantation 43% were still functioning (patient survival 76%); of those followed for 12 months,

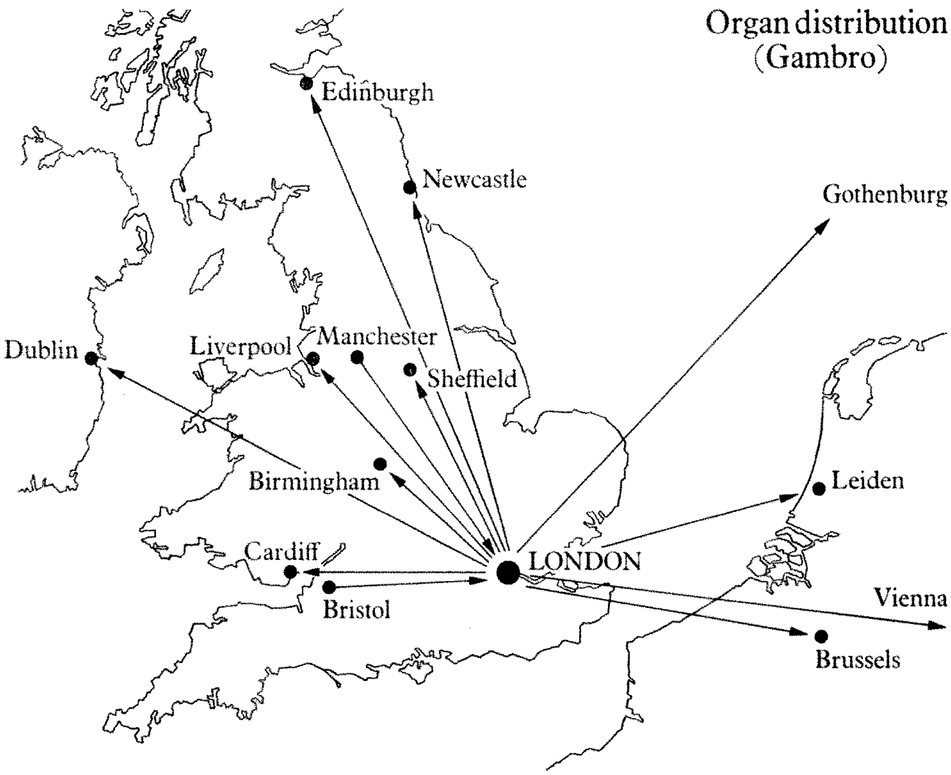


Fig. 3. Kidneys were distributed during preservation on the basis of tissue typing results.

47% were functioning (patient survival 78%); and of 30 kidneys transplanted more than 18 months ago, 50% were still functioning (patient survival 77%) (Table I).

Of the 16 kidneys that did not function, 6 were lost due to rejection, 4 due to arterial thrombosis, 2 due to haemorrhage in the postoperative period, 2 from early postoperative death, 1 from renal vein thrombosis and 1 from primary non-function in an apparently unviable organ.

A clear-cut correlation was demonstrated between kidney function and warm anoxia time (the time from cessation of respiration or ventilation to the time when the kidney was immersed in ice).

Table I

Survival Rates of Patients and Kidney Grafts in Months after Transplantation, following Kidney Preservation by Continuous Perfusion

	Months after Transplantation		
	6	12	18
Kidneys transplanted	51	45	30
Patient survival	76%	78%	77%
Kidney survival	43%	47%	50%

This was less clearly shown with the more commonly accepted criterion of warm ischaemia time (from circulatory arrest) (Table II).

Assessment of total cold ischaemia time showed that the average time to function increased markedly once the cold ischaemia time (C.I.T.) exceeded 12 hours (Table III)—which was a reflection of a similar increase once the total time the kidney was not being perfused exceeded 8 hours (including both pre- and post-perfusion cold ischaemia time) (Table IV). Non-function rate in these groups was unchanged. To assess whether a long period of perfusion was injurious, kidneys were divided into those perfused for more than and less than 12 hours, but time to function and non-function rate were similar in these groups (Table V).

Table II

Comparison of Warm Ischaemia Time and Warm Anoxia Time related to Time to Kidney Function in Days

Warm Ischaemia Time (min)	No. of Kidneys	Average Time to Function (days)	Warm Anoxia Time (min)	No. of Kidneys	Average Time to Function (days)
0-24	34	8	0-24	11	4·8
25-44	13	10	25-44	14	10·2
45+	3	14	45+	9	16·4

Table III

Average Time to Function and Non-function Rate related to Total Cold Ischaemia Time

Total Preservation Time (Cold Ischaemia)	No.	Average Time to Function (days)	No Discarded	Non-function %
0-12 hours	13	3·6	3	20
12-24 hours	43	10·8	8	32
24-36 hours	5	10·5	0	20

In most cases the preservation machine was taken to the recipient hospital and perfusion maintained until the kidney was transplanted. In 8 cases, however, the kidney was removed from the machine, replaced in ice and sent to the recipient hospital. Subjecting the kidney to a further period of non-perfused cold ischaemia slightly increased the average time to function and the percentage of non-function (Table VI).

An attempt was made to assess viability by observing flow rate during perfusion at a pressure of 60 mm mercury and by biochemical studies on the perfusate fluid. With flow rates over 100 ml/min no correlation could be made with average time to function, or graft failure rate (Table VII). Estimates at 30 min, 1 hour and the end of perfusion of SGOT, LDH, glucose, potassium and lactate showed no significant correlation with subsequent kidney function.

An analysis was made of 18 pairs of cadaveric kidneys one of which was preserved by continuous perfusion on the Gambro machine and the other by simple hypothermia. Each of these pairs of kidneys was taken from one cadaveric donor, and since the premortem damage to these pairs

Table IV

Average Time to Function and Non-function Rate related to Total Non-perfused Cold Ischaemia Time

Total Non-perfused Cold Ischaemia Time	No.	Average Time to Function (days)	No. Discarded	Non-function %
0-4 hours	20	6·6	3	25
4-8 hours	24	5·1	4	28
8-12 hours	13	14·6	3	20
> 12 hours	5	14·3	1	25

Table V

Average Time to Function and Non-function Rate related to Time on Continuous Perfusion

Perfusion Time	No.	Average Time to Function (days)	No Discarded	Non-function %
< 12 hours	37	9·0	9	22
12-27 hours	24	9·2	2	25

Table VI

Average Time to Function and Non-function Rate related to Presence or Absence of additional Post-perfusion Cold Ischaemia

Post-perfusion Cold Ischaemia Time	No.	Average Time to Function (days)	Non-function %
Nil	44	8	29
1-10 hours	8	12	38

of kidneys was the same, it might be anticipated that each of the individuals of a pair might behave in a similar fashion. Total preservation time for kidneys subjected to continuous perfusion averaged 17·4 hours as compared to a mean of 6·9 hours for kidneys preserved by simple hypothermia. The incidence of immediate function was similar with each of these preservation techniques and there was no reduction in the incidence of non-function as a result of the policy of discarding kidneys with poor perfusion characteristics (Table VIII). Furthermore, 3 of the kidneys in which the perfused paired organs were discarded subsequently functioned after a delay of 4 to 21 days. On the other hand, the fourth kidney failed to function.

Table VII

Average Time to Function and Non-function Rate related to Flow Rate during Perfusion

Flow (ml/min)	No.	Average Time to Function (days)	Non-function %	No. Discarded
0-100	13	...	(50)*	11
100-200	29	8·5	36	0
200-300	17	7·7	18	0
300+	4	12·0	25	0

* Only 2 kidneys in this group were transplanted, one of which was taken from a child.

Table VIII

Comparison of Simple Hypothermia and Continuous Perfusion in 18 Pairs of Cadaveric Kidneys related to Immediate Function and Non-function Rates

	Continuous perfusion	Non perfused
No. of kidneys	18	18
No. discarded	4	0
Immediate function	5/14 (36%)	7/18 (39%)
Non-function	2/14 (14%)	2/18 (11%)
Mean preservation time (hours)	17·4	6·9

Discussion

Continuous hypothermic kidney perfusion has been shown to be superior to other methods of preservation both experimentally (Belzer, Ashby and Dunphy, 1967; Moberg *et al.*, 1972), especially with a period of warm ischaemia (Johnson *et al.*, 1972), and in human kidney preservation (Miller, Alexander and Smith, 1973; Blohmé and Claes, 1973). The recent good results of canine kidney preservation using a hyperosmolar intracellular medium for initial perfusion (Sacks, Petritsch and Kaufman, 1973) have yet to be evaluated in human kidneys. In a collaborative study Clark *et al.* (1973) found that although the average preservation time was extended from 6 to 21 hours using continuous perfusion, the one-year survival and immediate function rates were significantly better with kidneys preserved by simple hypothermia. These conclusions, however, were disputed by other authors (Taylor, Johnson and Swinney, 1973; Belzer, 1973; McLoughlin, Sells and Tyrell, 1973; Miller *et al.*, 1973) who considered that the groups were not comparable, and suggested that simple hypothermia was only suitable for short term storage which did not provide sufficient time if widespread exchange of kidneys was necessary to obtain good HLA matching and for adequate preparation of recipients.

Our results show that continuous perfusion of human cadaveric kidneys allows the total preservation time to be extended up to 36 hours, allowing the transplantation operation to be performed as an elective procedure with checking of tissue typing and long-distance transportation. The best results as measured by time to function were obtained if the non-perfused CIT was less than 8 hours and if the total CIT was less than 12 hours. However, analysis showed that once the kidney was being continuously perfused the preservation time could be extended up to 27 hours without additional ischaemic damage. On the other hand, the results were most favourable if the period of warm ischaemia was less than 25 minutes, particularly if measured from the time of respiratory arrest. Assessment of viability by measurement of flow rate and biochemical studies appeared unreliable and some kidneys were discarded which might have functioned had they been transplanted. Comparison of the function of continuously perfused kidneys with unperfused pairs showed that immediate function was not increased and the non-function rate remained unchanged. Thus there was no evidence that continuous perfusion produced significant resuscitation of damaged cadaveric kidneys. It may be concluded that continuous perfusion of cadaveric kidneys by this technique simply extends the preservation time.

Summary

63 cadaveric kidneys have been preserved for up to 36 hours by continuous perfusion on a Gambro machine. 52 kidneys were transplanted: 13 (25%) functioned immediately, 23 (44%) functioned after 2 to 28 days, and 16 (31%) failed to function. 11 kidneys with poor perfusion flow characteristics were discarded. Of 30 kidneys followed for more than 18 months, graft survival was 50%.

Analysis of warm and cold ischaemia data, of perfusion flow rates and biochemical studies, and comparison of function of 18 pairs of kidneys only one of which was continuously perfused, suggests that this method of preservation effectively extends the preservation time to 36 hours, but does not improve the immediate function and non-function rates, and does not provide an accurate assessment of viability.

We wish to thank the staff of the transplantation units of the following hospitals for kindly providing information on the function of the kidneys: Queen Elizabeth Hospital, Birmingham; Jervis Street Hospital, Dublin; Western General Hospital, Edinburgh; Sahlgrenska Sjukhuset, Gothenburg; Academisch Ziekenhuis, Leiden; Charing Cross, Guy's, Hammersmith, The London, Royal Free, and the Westminster Hospitals, London; and the Royal Victoria Infirmary, Newcastle upon Tyne.

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A Study of 137 Cases of Renal Trauma

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Renal injuries are rarely a threat to the patient's life, and interest in their management centres around preserving renal function and lessening morbidity. The conservative management of closed renal injuries is successful in the majority of patients, as has been shown by Slade (Slade, 1971). In America there appears to be a trend towards a more aggressive approach with immediate angiography and surgical exploration (Halpern, 1968; Villar, Ireland and Cass, 1972).

Comparison between the different methods of management is difficult owing to the wide range of renal injuries sustained and the presence of life-threatening associated injuries. This retrospective study was undertaken in order to assess the possible need for arteriography and to review the results obtained with conservative management. The findings are in accord with those of Vermillion, McLaughlin and Pfister (1971) and Withycombe (1974), and confirm the merits of conservative treatment described by Slade (1971).

The Patients

There were 137 admissions of patients with renal injuries to King's College and Lewisham Hospitals in the period 1958-72. Only one of these injuries was a penetrating one. The injuries have been classified into 3 groups according to the severity as judged radiologically (Table I). The radiological abnormalities seen in the moderate injuries reverted to "normality" whereas the patients in the severe group were left with scarred kidneys and an abnormal urogram.

Table I

Classification of Renal Injuries

Severity of Injury	Initial Intravenous Urogram shows	Number
Mild	No abnormality	73
Moderate	Minor abnormality but all collecting system visible	40
Severe	Major abnormality, *e.g.* some or all of collecting system not visible	22
Total		137

In each of the 3 groups males predominated (82%) and 75% of all patients were under 30 years of age. Road accidents and falls each accounted for one-third of the injuries, whilst sport and fights accounted for 21% and 10% of injuries respectively. Severe injuries were associated with the highest incidence of macroscopic haematuria (86%), hypotension (27%) and the presence of a palpable mass in the loin (18%). Right-sided injuries occurred more frequently in severe injuries

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(24% in mild, 30% of moderate and 41% of severe) and 5 patients had pre-existing renal pathology (3 hydronephrosis, renal stones and tumour).

In both hospitals the essence of management was conservative. Patients were confined to bed until the haematuria had ceased and intravenous fluids and blood transfusions were given as indicated. Antibiotics were not given prophylactically, but 36 patients required them for a variety of reasons (17%, 30% and 50% in each group respectively). There were no problems with infection or secondary haemorrhage in the series and there is little evidence elsewhere that prophylactic antibiotics are of benefit in renal injuries.

Early renal exploration was performed on 12 occasions and the 8 nephrectomies will be discussed subsequently. An additional patient had a nephrectomy for a tumour which was diagnosed some months after his initial presentation.

It is difficult to assess the morbidity of renal injuries, but some indication may be gained from the duration of hospitalisation as is shown in Figure 1. In some instances the stay was prolonged by the associated injuries, but this will be discussed for each group of injuries.

An attempt was made to trace each of the Lewisham patients for the purpose of this follow-up, and those seen were examined, urine microscopy performed and an intravenous urogram obtained. Only 45% of the patients with mild injuries attended, but this is not surprising as many of them failed to attend at all after discharge from hospital. In marked contrast, only 1 of the 8 patients with severe injuries failed to attend for follow-up. In the King's College Hospital group of patients an attempt was made to follow up these patients with moderate or severe injuries, but only 50% of these attended.

Mild Renal Injuries

The management of patients in this group is straightforward and presents few problems. 14 of the 75 admissions did not have an intravenous urogram—2 had a laparotomy for intraperitoneal injuries and the remainder failed to attend for out-patient investigation. The remaining 61 patients had normal urograms and no evidence of any subsequent trouble was found in the 20 patients who were traced for the late follow-up.

Eleven (14%) patients with mild renal injuries stayed in hospital for more than 2 weeks, but in only 5 patients was the prolonged stay due to the renal trauma. In general, there has been a tendency towards earlier mobilisation and discharge. The persistence of macroscopic haematuria for more than 7 days, despite a normal intravenous urogram, is an indication for further investigation by renal arteriography; other causes of haematuria should be considered. If the arteriogram is normal, the patient should be mobilised.

An interesting group of patients are those with the Munchausen Syndrome. A long-distance lorry driver was admitted to King's College Hospital in 1958, again in 1963 and to Lewisham in 1964. He was also admitted by one of us in Doncaster in 1966 and he has undoubtedly visited many of your hospitals. He is easily recognisable by his scarred abdomen! He complained that he had struck his abdomen against the steering wheel and had haematuria. This was never substantiated, and despite the history of a previous partial nephrectomy, his intravenous urogram was normal.

Moderate Renal Injuries

The 40 patients in this group had more severe injuries radiographically, but on clinical grounds they differed little from those with mild injuries. The radiological abnormalities of the collecting system were reported as "delayed opacification (9)[1] or the presence of clot (8). Spastic calyces (4), enlargement or blurring of the renal outline (4), or extravasation of urine (4) were sometimes observed. In all these patients the calyces were visible, although the presence of gas often rendered this less than perfect. In this group the intravenous urogram was subsequently reported as having

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[1] Numbers in brackets refer to the number of occasions each abnormality was observed.

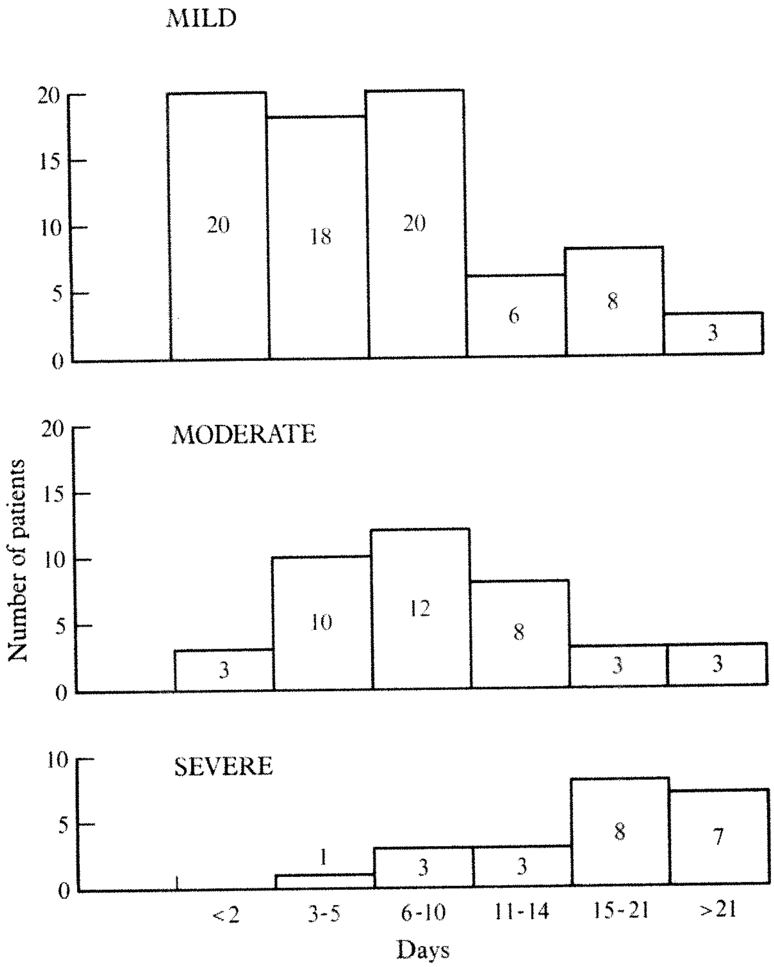

Fig. 1. Duration of hospitalisation with renal injuries.

returned to normal, although on close inspection it was still possible to detect minor abnormalities on some occasions.

Conservative management was abandoned on 2 occasions in this group, once without good cause and the registrar drained the renal bed. The other patient had been stabbed and arterial bleeding from the upper pole was controlled by suturing. The only nephrectomy in this group was performed in a patient with an invasive transitional cell carcinoma. The radiological appearance was suggestive of polycystic disease and earlier arteriography would have saved the delay of many months. One other patient was explored for a pre-existing pelviureteric junction obstruction, but this was not related to his injury.

The threat to renal function is small in patients with moderate injuries and the patients were discharged from follow-up when the urogram had returned to normal. None of the 10 patients with moderate injuries who attended for follow-up exhibited any complications.

Figure 1 shows that patients with moderate injuries tended to stay in hospital longer than those with minor injuries. 6 patients stayed in longer than 14 days and the demonstration of a normal renal arteriogram encourages their early mobilisation, whereas the demonstration of a fractured kidney encourages caution.

Severe Renal Injuries

This group differs from the preceding ones on both clinical and radiological grounds. 1 patient had a laparotomy within 15 minutes of his arrival on account of massive haemorrhage from his liver. He also had a shattered kidney which was removed at the conclusion of his partial hepatectomy. The intravenous urograms in the remaining patients all showed complete or partial non-visualisation of the injured kidney. In none of these patients did the urogram return to "normal".

4 patients initially had a non-visualised kidney and one of these required an emergency nephrectomy for haemorrhage. The initial urograms in 2 patients showed a return of function to part of the kidney with the subsequent development of localised areas of renal atrophy. These patients have remained well over the succeeding years. The fourth patient was explored for persistent non-function and was found to have a ruptured hydronephrosis due to long-standing pelviureteric junction obstruction. A nephrectomy was performed.

We consider that an intravenous urogram is mandatory for all patients admitted with renal injuries and any patient with a non-visualised kidney should have an immediate renal arteriogram. This is essential if injuries to the renal vasculature are to be detected early enough for successful conservative surgery.

In the remaining 17 patients part of the injured kidney was not visualised but extravasation of contrast medium was only seen in 4 patients. 7 patients were operated upon for haemorrhage and on 3 of these a splenectomy was performed. In 2 of these patients, the kidney was explored but not removed, but in the third the kidney was removed with little justification. We consider that during the course of a laparotomy for trauma a retroperitoneal haematoma should be left alone unless it is increasing in size.

In summary, 10 of the 22 patients with severe renal injuries required operation and a nephrectomy was performed on 8 occasions. These nephrectomies were carried out within the first 48 hours after admission and there were no secondary haemorrhages or infected haematomas despite the lack of prophylactic antibiotics. Conservative management was successful in more than half the patients although in many patients part of their kidneys atrophied without the development of hypertension. Angiograms performed in 5 of these patients suggest that the kidneys were as severely damaged as some of those removed.

The ischaemic renal cortex fibrosis to give a characteristic appearance on subsequent urograms, but there is no evidence to suggest that it predisposes to the development of hypertension. This finding of Slade's (1971) was confirmed in the present study.

Severe renal injuries were associated with a greater morbidity and it is difficult to say whether a nephrectomy shortens the period of hospitalisation. 4 of the 8 patients having a nephrectomy were in hospital more than 21 days, but only 3 of those treated conservatively stayed longer than that length of time.

What is the role of arteriography in severe renal injuries? It is mandatory in all patients where the initial intravenous urogram shows a non-functioning kidney. If the kidney shows only partial function, we believe that arteriography should be performed to define the extent of renal parenchymal damage. Should operation become necessary on clinical grounds, it might facilitate conservative surgery. It is doubtful whether arteriography will predict which patients may bleed and require exploration.

Summary

Renal injuries are rarely a threat to life and all patients should have an intravenous urogram performed at the time of admission.

Patients with a normal urogram may be mobilised for early discharge.

Patients with minor abnormalities of the urogram, but in whom all the collecting system is visible, rarely caused any difficulties in management. Should the haematuria persist beyond a

week, then arteriography should be performed. The arteriogram sometimes shows the presence of major cortical lacerations with minor abnormalities of the intravenous urogram.

If the initial urogram fails to opacify the injured kidney, immediate arteriography is required to exclude a vascular injury. We also believe that early arteriography is advisable in those patients where part of the kidney appears to be non-functioning as it is in this group of patients that operation may become necessary. The indications for renal arteriography are summarised in Table II.

Table II

Indications for Arteriography in Renal Trauma

1. Immediate	Complete Partial	visualisation on intravenous urogram
2. Early	Prolonged haematuria Poor visualisation Uncertain pathology	
3. Late	Hypertension Arteriovenous-fistula	

We would like to thank the surgeons who cared for these patients for their permission to study them and Miss Heather Ironmonger for typing the script.

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Ultrasound in the Staging of Bladder Tumours

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At the Annual Meeting of this Society in 1971, a report on the use of diagnostic ultrasound in the investigation of the urinary tract was presented (Kyle *et al.*, 1971). In particular, the application of ultrasound to the diagnosis of kidney and bladder tumours was discussed.

Material and Methods

The equipment, a prototype version of the Diasonograph 4101, remains the same, and the scanning technique described by Barnett and Morley (1971) is likewise unchanged. A non-storage oscilloscope is used for recording purposes, photographs of two-fifths size are taken on polaroid film.

An attempt has been made to assess what place, if any, ultrasonic examination has to play in the investigation of tumours of the bladder, with particular reference to the staging of these tumours. Its accuracy has been compared with that obtained by the standard methods of clinical bladder tumour staging. No attempt has been made to use this investigation as a means for screening cases of suspected bladder tumours, and apart from a few cases all tumours were confirmed by endoscopy, prior to ultrasonic scanning.

Findings

The appearance of the urinary bladder on ultrasound examination is already familiar to many urologists, but a brief account of the more typical findings is presented, and some of the scans obtained are reviewed. The normal bladder shows a typically quadrilateral appearance on the low transverse scan (Fig. 1). The value of the longitudinal scan is most readily appreciated in the localisation of tumours of the posterior bladder wall and base. Tumours close to the bladder neck can be difficult to outline satisfactorily, but it is to be hoped that rectal probes will overcome this problem (Watanabe, H. *et al.*, 1971).

Multiple low-grade tumours give an impression of mucosal irregularity without distortion of the normal bladder shape (Fig. 2), but these tumours on many occasions are difficult to see on ultrasound examination. Larger non-infiltrating tumours are more readily outlined (Fig. 3). Infiltrating tumours usually cause changes in the bladder wall with distortion of the normal ultrasound appearance, (Fig. 4) and in many cases give rise to a diminution of normal bladder capacity. This finding may be accompanied by increased bladder irritability, not an uncommon finding particularly when infection is present.

Extravesical spread shows the features of invasive tumours within the bladder wall, and in addition changes in the paravesical pelvic tissues (Fig. 5). These changes suggest distortion of the normal echo pattern and their ultrasonic characteristics should be accepted as the typical echographic appearance of tumour infiltration. From our findings on ultrasound examination it is possible to categorise the appearances that have been described above into 3 main groups.

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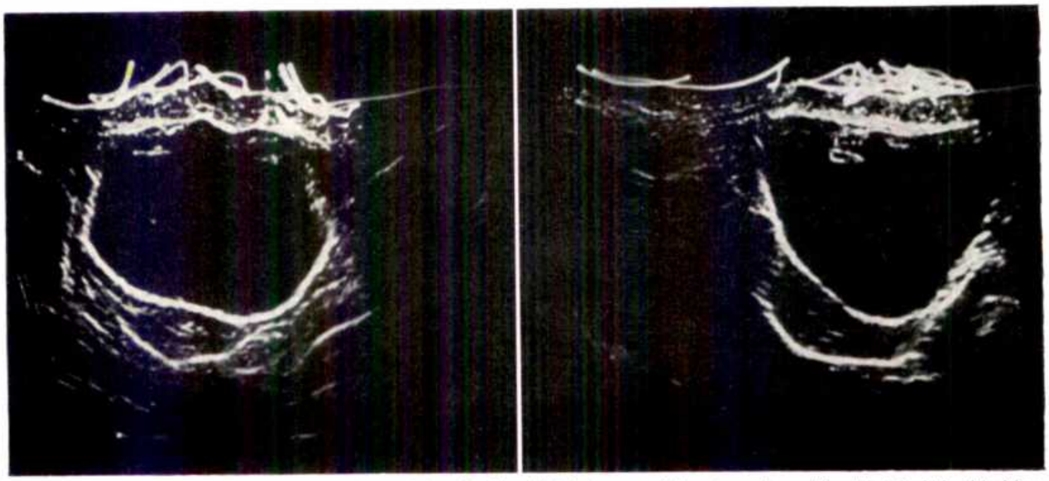
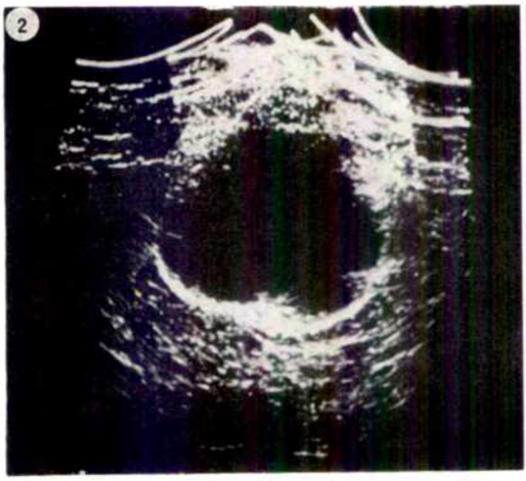


Fig. 1. Normal bladder in transverse (left) and longitudinal (right) scans. The uterus is outlined behind the bladder.



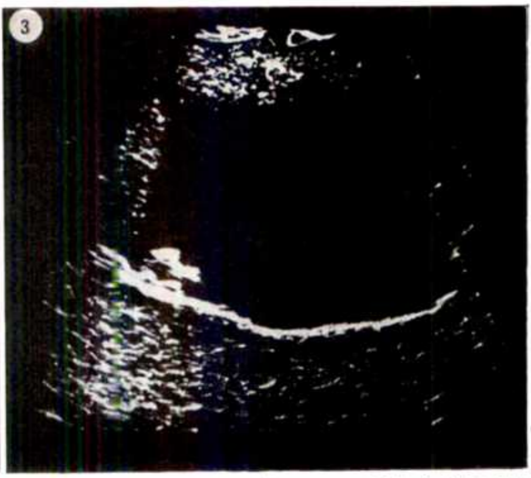


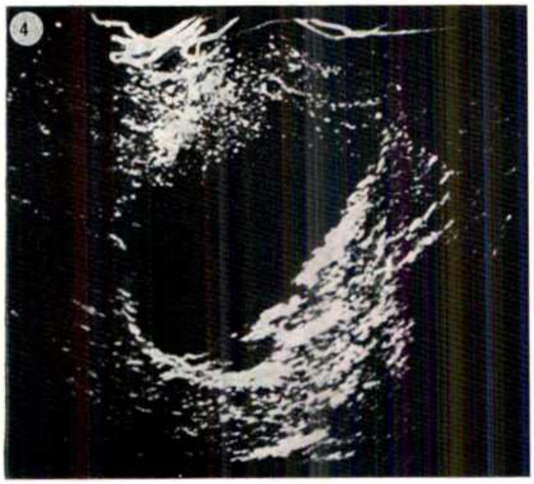
Fig. 2. Small multiple superficial bladder tumours. (Transverse scan.) Reproduced from "Barnett and Morley" (1974) by courtesy of Butterworths.

Fig. 3. Pedunculated papillary bladder tumour of right posterior bladder wall. (Transverse scan.)

Table I summarises these findings, showing the typical appearances in each group of tumours.

The tumours that have been referred for ultrasound investigation have all been staged by accepted diagnostic means. These comprise intravenous urography, cystoscopy, biopsy and bimanual pelvic examination under anaesthesia. Histological material, obtained at endoscopic biopsy and at operation, has been used to alter the impression of clinical staging, when definite pathological evidence of invasion has been seen. It is accepted that endoscopic biopsy frequently renders tissue of a superficial nature, only the degree of differentiation being readily appreciated by the pathologist.

All tumours have been staged by means of the TNM classification of the UICC, and each staging has been compared with its ultrasound appearance in order to establish whether or not there is any reliable correlation between the two. The total number of tumours available for study was 197 (Table II). Of these, 162 were tumours referred at the time of initial presentation. 26 were



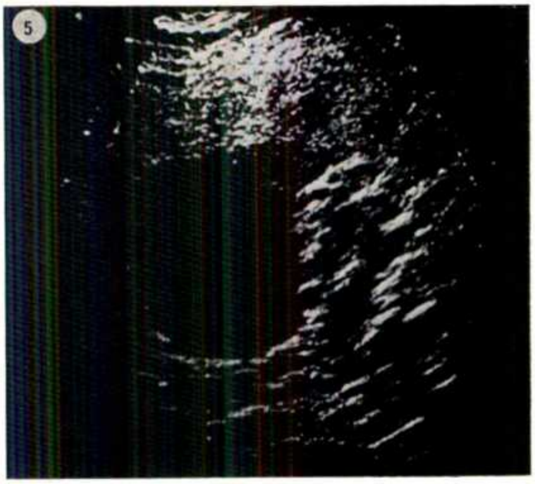


Fig. 4. Extensive invasion of the left bladder wall by a very flat tumour, causing asymmetry of bladder outline. There is no evidence of paravesical spread. (Transverse scan.)

Fig. 5. Massive tumour involvement of the left wall of the bladder with evidence of invasion of the paravesical soft tissues extending to the lateral pelvic wall. (Transverse scan.)

Table I

Diagnostic Ultrasound Features of Bladder Tumour

	Bladder	Pelvis
Group A	Tumour outline	Normal
	Normal capacity	
	Fully expansile	
Group B	Tumour outline	
	Rigid wall	Normal
	Reduced capacity	
Group C	Loss of continuity of bladder wall	Abnormal pelvic echoes
	Outline	Large pelvic mass
	Reduced capacity	

Table II

Analysis of Cases

1. New untreated tumours	
T_1	40
T_2	92
T_3	30
2. Previously treated tumours	26
3. Secondary spread to bladder from other pelvic tumours	9
Total	197

cases that had been referred with recurrent tumours following endoscopic resection or diathermy at other centres.

In 9 instances there was secondary bladder involvement by tumour spread from other pelvic organs.

Only those cases of primary bladder tumour referred for ultrasonic examination at the time of initial diagnosis have been presented. These 162 cases will now be discussed in further detail.

T_1 Tumours

40 T_1 tumours were referred for ultrasonic examination (Table III). This is a small proportion (25%) of the total 162 cases. This is explained on the grounds that many of these superficial tumours were diagnosed, biopsied and resected at the initial cystoscopic examination, thus precluding them from ultrasonic assessment.

On the basis of the ultrasonic features already described, 25 T_1 tumours with group A characteristics were found. It is postulated that these characteristics are those typical of T_1 tumours. 11 tumours thought clinically to be T_1 had the appearance of Group B. In 4 cases the examination was unsuccessful and these will be discussed, along with other failures, later.

An accuracy of 70%, when failed investigations were excluded, was obtained.

Table III

T_1 Tumours

Total number of tumours		40
Staging correct	25	
Over staged	11	
Failed investigation	4	
Accuracy		70%

Table IV

T_2 Tumours

Total number of tumours			92
Staging correct		62	
Errors		9	
Understaged	5		
Overstaged	4		
Failed investigations		21	
Accuracy			87%

T_2 Tumours

In all, 92 tumours clinically staged as being T_2 (Table IV) had ultrasonic examination and of these 62 were found to have the typical changes seen in Group B. 5 cases showed the appearances of Group A, being deemed to be ultrasonically understaged, and 4 showed the features of Group C and therefore overstaged.

In 21 instances the examination was unsuccessful.

An overall accuracy of 87% was therefore obtained when dealing with T_2 tumours.

T_3 Tumours

30 T_3 tumours were examined (Table V) and correctly assessed ultrasonically in 19 cases. In 4 instances the tumours were, by our criteria, understaged. An accuracy of 83% was therefore obtained when 7 failures were excluded.

Out of 162 tumours examined by ultrasound, there were 32 cases (20%) that for various reasons did not give satisfactory scans.

Table VI shows the number and various causes of failed investigations. Reduced bladder capacity, generally accompanied by marked detrusor irritability, was the commonest problem, contributing 18 to the total number of 32 failures. When it is seen that 17 out of the 18 cases had tumours staged clinically in T_2 or T_3, this particular cause of difficulty can be regarded as a poor prognostic sign.

Table V

T_3 Tumours

Total number of tumours		30
Staging correct	19	
Understaged	4	
Failed investigations	7	
Accuracy		83%

Table VI

Failed Investigations

T_1	4		
T_2	21		
T_3	7		
	—		
Total	32		
Causes:		Obesity	2
		Small capacity	18
		Blood clot	2
		Technical difficulty	6
		Detail obscured by catheter	3
		Unprepared patient	1

Obesity gives rise to some difficulty and the hope that tumour staging in overweight patients might be simplified by ultrasound, where difficulty in bimanual assessment has been encountered, has not been upheld. Blood clot within the bladder causes difficulty in interpretation when it obscures the tumour. A number of cases required to be examined in the presence of an indwelling, generally balloon type, catheter. This also gives rise to diagnostic problems, but in only 3 cases were these sufficient to invalidate the examination. Technical difficulty was experienced in 6 cases, chiefly due to the problems experienced in scanning tumours around the bladder neck. Also, there were a small number referred prior to endoscopy, where difficulty in localising the position of the bladder tumour was encountered.

It was thought justifiable, when assessing the overall accuracy of ultrasound, to exclude those cases where the examination could not be concluded, as no ultrasonic staging was given to these tumours.

In assessing what place, if any, ultrasound investigation holds in the clinical staging of bladder tumours, it has been necessary to compare its accuracy with that obtained by other radiographic techniques (Table VII). It can be seen that the only method that gives comparable results, as far as accuracy is concerned is the use of arteriography, in conjunction with the use of perivesical and endovesical gas.

Table VII

Comparison with other Radiological Techniques

	Taylor (1965)	Cornell (1967)	Lang (1969)	Lacy (1970)	
	%	%	%	%	
Cystoscopy	...	...	60	...	
Cystogram	...	...	50	...	
Superimposition cystogram	...	...	50	...	
Double contrast cystogram	...	...	56	...	
Arteriography, peri- and endovesical gas	93	87	88	95·5	
Ultrasound	...	...	...	...	80%

Comparing this with the accuracy achieved ultrasonically, one can see that the triple contrast method is superior, but this superiority is achieved at the expense of discomfort and hazard to the patient together with the technical problems of the procedure itself. The accuracy of both methods is compared in Table VIII.

Table VIII

Comparison with Triple Contrast Radiography

	Arteriography, Perivesical and Endovesical Gas (Lang, 1969)	Ultrasound
	%	%
Mucosa	66⅔	70
Submucosa	80	
Superficial muscle	75	87
Deep muscle	75	
Peri-vesical spread	91·7	83
Other organs	75	

Summary

The ultrasonic features of 162 bladder tumours are described.

Comparing clinical staging by the TNM system and the ultrasonic appearances, there is a high degree of accuracy in staging by ultrasound.

The use of this painless non-invasive technique is assessed and should be used in staging bladder tumours only in conjunction with other established methods, and not in isolation.

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A Critical Review of the Management of Bladder Neoplasia using a Modified Form of Helmstein's Pressure Therapy

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Growths of the bladder have been treated by many different methods over the years with varying degrees of success. Helmstein (1966) introduced a new approach to carcinoma of the bladder in which the intravesical pressure was raised continuously for several hours, so reducing the blood flow through the bladder and causing tumour anoxia. Malignant cells are thought to have a higher metabolic rate than normal bladder epithelium, so necrosis should occur more readily in tumour tissue.

Helmstein's results (1971, 1972) and those of England *et al.* (1973) confirm tumour destruction by this method. The object of this communication is to assess the result of this technique in a selected group of patients who all had vesical neoplasms proven on biopsy.

Patients

30 patients underwent treatment, in 8 of whom the procedure was repeated. 9 of these were women and 21 men with an average age of 66·2 years. 1 patient refused follow-up, but was known to be alive and symptom-free 9 months following his treatment and, since no follow-up is available, he has been excluded from the results, 29 patients forming the basis of this report. The follow-up period has varied, the minimum being 8 months and the longest 21 months.

All patients had intravenous pyelography, urine culture and cytology performed before treatment. Cystoscopy, biopsy of the tumours and bimanual assessment of the clinical stage of the tumours were all carried out by the author personally. The clinical staging of the tumours was according to the IUCC 1962 method of classification, the details of which are shown in Table I. Post-treatment cytology, cystoscopy and further biopsies at regular intervals were carried out as a routine. Initially, follow-up cystoscopic examination was done 1 week after treatment to confirm necrosis. It became obvious that, if a cystoscopy was carried out too soon, it was impossible to

Table I

Clinical Staging of Bladder Tumours (IUCC 1962)

Sex	T_1	T_2	T_3	T_4	Total
Female	4	4	...	1	9
Male	6	5	6	4	21
Total	10	9	6	5	30

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decide how much necrosis had occurred, as it takes several weeks for the slough to separate, particularly if the growths were bulky. The ideal time for a check cystoscopic examination would appear to be between 6 and 8 weeks. 2 patients, who were in the terminal stages of the disease, died without follow-up cystoscopies. Therefore, 27 patients were adequately assessed after the therapy by cystoscopy and biopsy.

A few patients had pelvis angiograms and lymphangiograms but these were discontinued as they were found to be unhelpful. Double contrast cystograms were used towards the end of the series and were very useful in assessing the degree of necrosis in bulky tumours.

Technique used in Double Contrast Cystography

1. The patient is catheterised and the bladder drained.
2. 50 ml of sterilised barium suspension (Steripaque) are injected through the catheter and the patient rotated through 360° to coat the bladder wall.
3. Excess medium is drained off, leaving a barium coated mucosa.
4. Carbon dioxide is injected through the catheter which produces a dark background and distends the bladder. The tumour stands out as a filling defect. Up to a litre of CO_2 can be used but pressure has been kept deliberately low after treatment, and good contrast has been obtained with as little as 200 ml. A special reduction valve on the CO_2 cylinder allows easy filling of a syringe through sterile tubing.
5. Films are taken during screening with both barium and gas injections being done under screen control.
6. A.P., P.A., oblique, lateral and erect films are taken the views being modified by the site of the tumour.
7. The bladder is drained and flushed out with normal saline.
8. Carbon dioxide is used as it will not cause fatal gas embolus.

Method

The author had the privilege of meeting Helmstein and observing him treating patients at his clinic in Stockholm in 1972 and, for the first 6 cases, his technique was followed exactly as described (Helmstein, 1972), using a rubber balloon. His alternative technique of using a Foley catheter and filling the bladder with saline has not been attempted. After the first 6 cases, the introduction of the balloon into the bladder was modified and is described elsewhere (Glashan and Brown, 1974). Epidural anaesthesia was used in all cases but it was found that two separate injection sites were preferable to remove all bladder stimuli and also to depress and stabilize the diastolic blood pressure (Brown, Arthurs and Glashan, 1974). In all cases, the treatment was maintained for a minimum period of 6 hours after the bladder had been initially distended. When the treatment was concluded, the infusion set was disconnected, the bladder emptied and the balloon removed. In 2 cases it was found that the balloon had, in fact, ruptured but this produced no ill-effects in the patient. A self-retaining catheter was then inserted into the bladder and continuous drainage instituted for 3 to 4 days, during which time masses of grey necrotic material passed through the catheter. In all cases the patient resumed normal micturition and was usually able to leave hospital about 5 to 6 days following treatment.

No immunological studies were done in this series.

Pressure. The balloon pressures in the series were standardised as follows.

Using the pubic symphysis as a fixed point, and with a diastolic blood pressure lowered to 60 mm Hg, the equivalent pressure in cm of H_2O was found by multiplying 1·4 (specific gravity of Hg = 13·6) giving an approximate value of 84 cm of H_2O.

In addition, to allow for the distensibility of the rubber balloon, a further 25 cm of H_2O was added and so an initial starting pressure as measured by the height of the saline reservoir above the pubic symphysis was of the order of 110 cm of H_2O.

Results

After treatment all patients were assessed in response to the following questions. (1) Did necrosis occur and, if so, to what extent? (2) Were the patients' symptoms relieved? (3) Was there any evidence of undesirable side-effects? (4) What is the place, if any, for this form of therapy in bladder neoplasms?

There were no deaths as a direct result of the distension therapy and there was no case of rupture of the bladder, although 1 patient may well have had a partial leakage of saline as his bladder did fill up very rapidly in the later stages of treatment. The treatment did not upset the patients in any way and even when repeated in 8 patients there were no apparent ill-effects.

In all cases there was some degree of necrosis, 8 out of the 29 patients being completely clear of tumour in the immediate follow-up period (that is within 10 weeks). However, when one assesses the patients to find out how many responded well to the therapy and had a good result from the treatment, an entirely different pattern emerges. Partial necrosis is not necessarily a failure because, in 6 cases, massive necrosis actually occurred although there were still remnants of tumour tissue left. Reviewing the whole series of 37 treatments, 28 treatments showed a substantial improvement and were obviously worth while, while in 9 treatments it is doubtful if there was any real benefit although there was some necrosis present. Table II and III illustrate the response to treatment according to the tumour staging, showing a good response in the T_1 and T_4 groups while in T_2 and T_3 the response was poorer.

Table II

Response to Treatment

Stage	No. of Patients	No. of Treatments	Good	Poor
T_1	9 (10 – 1)*	12	11	1
T_2	9	11	7	4
T_3	6	7	4	3
T_4	5	7	6	1
	29	37	28	9

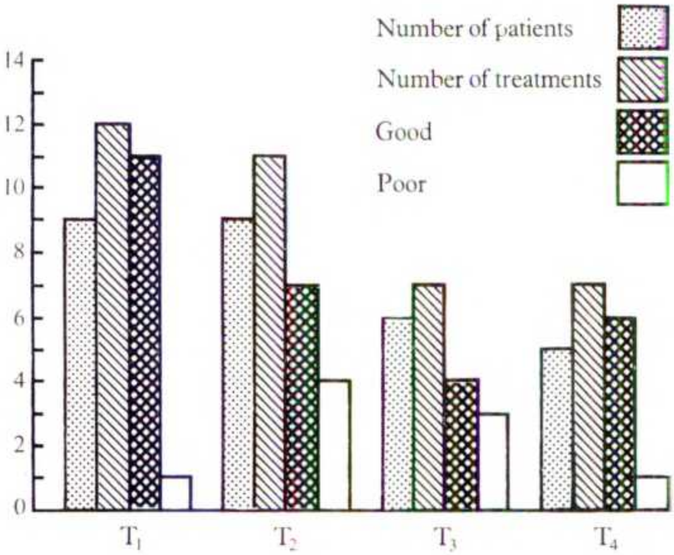
* 1 not followed-up.

Figure 1 demonstrates a T_1 tumour as it was photographed through the cystoscope. Histologically it was shown to consist of non-invasive papillomata. 6 weeks after treatment, total necrosis had occurred and the bladder appeared clear of all tumour but the bladder wall was rather pale (Fig. 2). Histologically, biopsy of the bladder wall showed chronic inflammation with some areas of calcification (Fig. 3). Areas of calcification were noted on several post-treatment biopsies but the significance of this is unknown. Figure 4 shows infarcted tumour with non-viable malignant cells under high power. Figure 5 is a histological section showing necrotic tumour, deep to which there is viable tumour cells in the muscle. This biopsy was from a T_3 tumour, where there was apparently a good response to the treatment on cystoscopy and serves to illustrate that, although there may be massive necrosis, viable tumour cells can still be left in the deeper layers in the muscle. A further section from the same patient shows necrotic tissue with tumour in the lymphatics which, of course, could not be observed at cystoscopy and therefore, although apparently there was a good response by this tumour, in fact, there was lymphatic involvement in the bladder wall (Fig. 6).

Cytologically, Figure 7 shows malignant cells altered within 5 days of treatment. A marked inflammatory response can be seen with polymorphs, histiocytes and changed malignant cells. The malignant cells themselves actually show some inflammatory change as well as disintegration

Table III

Response to Treatment



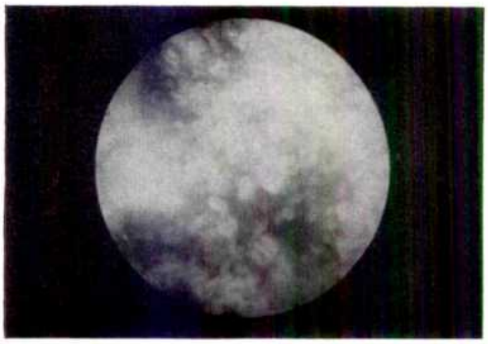


Fig. 1. Cystoscopic view of tumour before treatment.

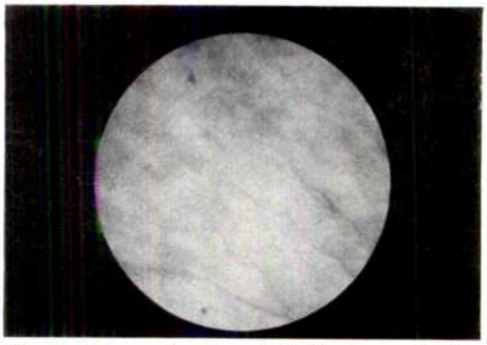
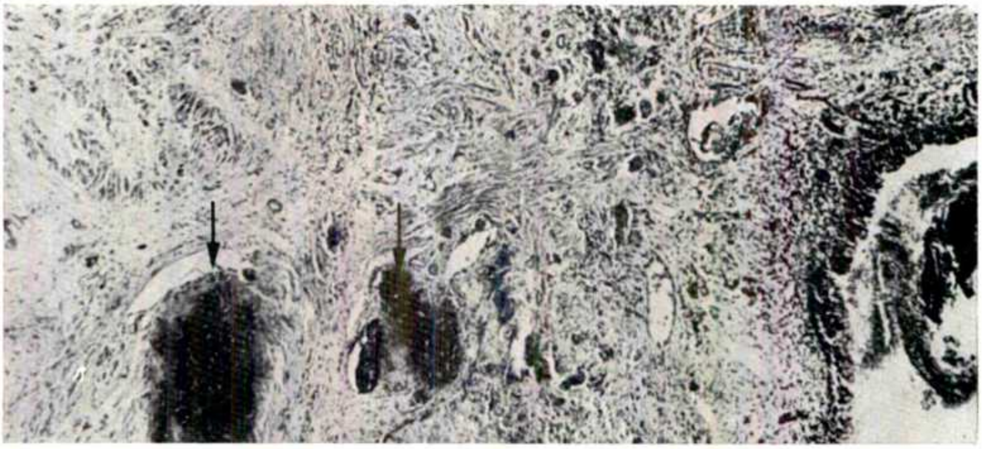


Fig. 2. Cystoscopic view of bladder 1 month after treatment.

and the use of cytology in the immediate post-treatment period can give an early indication as to whether necrosis has occurred.

A double contrast cystogram can be used to show reduction in the tumour mass and Figures 8 to 10 show a bladder before treatment, 10 days after treatment and finally at 3 months, cystoscopically the bladder being clear of tumour. In this particular patient there was a recurrence of tumour 5 months following treatment, but this was resected without difficulty and the bladder has been clear of tumour now for a further 6 months.

Although it is useful to know that necrosis has taken place following treatment, cystoscopy is best deferred for at least 6 to 8 weeks to assess fully the extent of the necrosis which occurs. It was noted that around the necrotic tumour areas, raised reddened patches of bladder mucosa were seen which correspond to the chronic inflammatory response known to occur as a result of this form of treatment. This, presumably, is due to the response of the bladder tissue to the necrosis



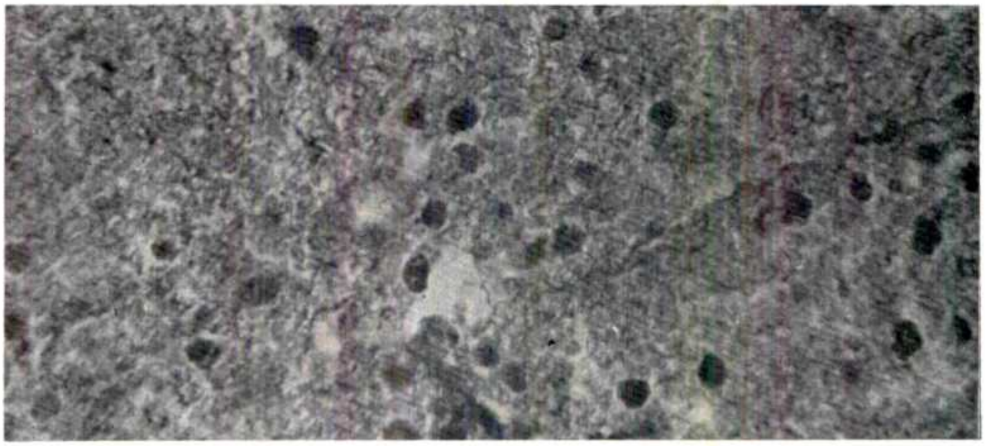


Fig. 3. Post-treatment biopsy showing chronic inflammation and calcification. H & E. ×10.

Fig. 4. Infarcted tumour with non-viable malignant cells. H & E. ×100.

which occurs and biopsies indicate that this is a chronic inflammatory reaction. It is very difficult to assess the depth of the necrosis, but, as has been shown by double contrast cystography, large tumour masses can be greatly reduced in size. Biopsies have shown definite areas of malignant cells deep to the necrosis, which suggests cystoscopy is not an entirely reliable method of determining the extent of necrosis and so where one suspects invasive T_2 and T_3 tumours, it is reasonable to suppose that viable tumour has been left behind. Accordingly, this method of treatment cannot be recommended for tumours which fall into these groups. In T_1 tumours, the cystoscopic appearances are helpful where basically the tumour is of a superficial nature, the best response in these cases being in the large bulky tumours. This corresponds with the findings of England *et al.* (1973). In the T_4 group, of course, where palliation only is being sought, superficial necrosis is the most that one could really expect and in the 5 cases that fall into this clinical stage in this series, all the necrosis was superficial in nature. This does not confirm the findings of Helmstein (1972).

Recurrence Rate. In this series when the tumours were followed up over a period of time, it became obvious that 8 of 9 T_2 tumours recurred and had to have further treatment, only 1 case remaining

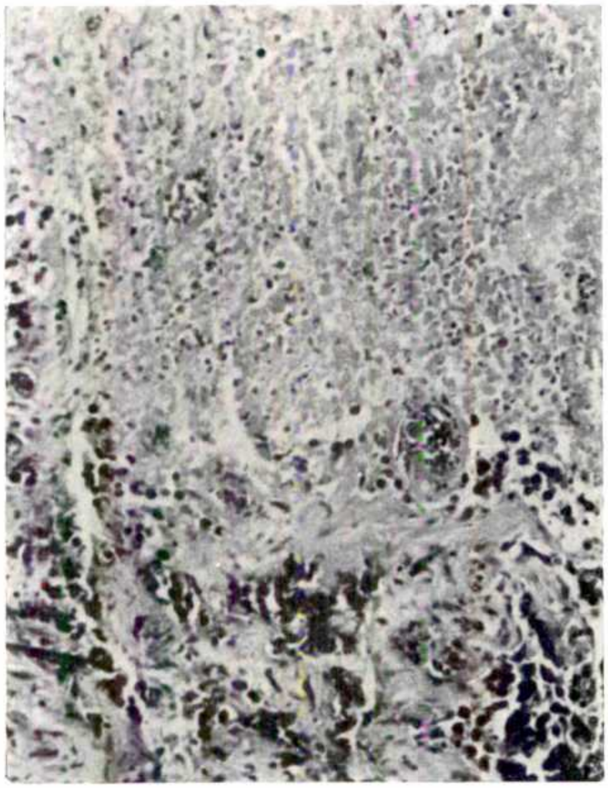


Fig. 5. Stage IV tumour showing superficial necrosis with viable malignant tumour in the deep layers. H & E. ×40.

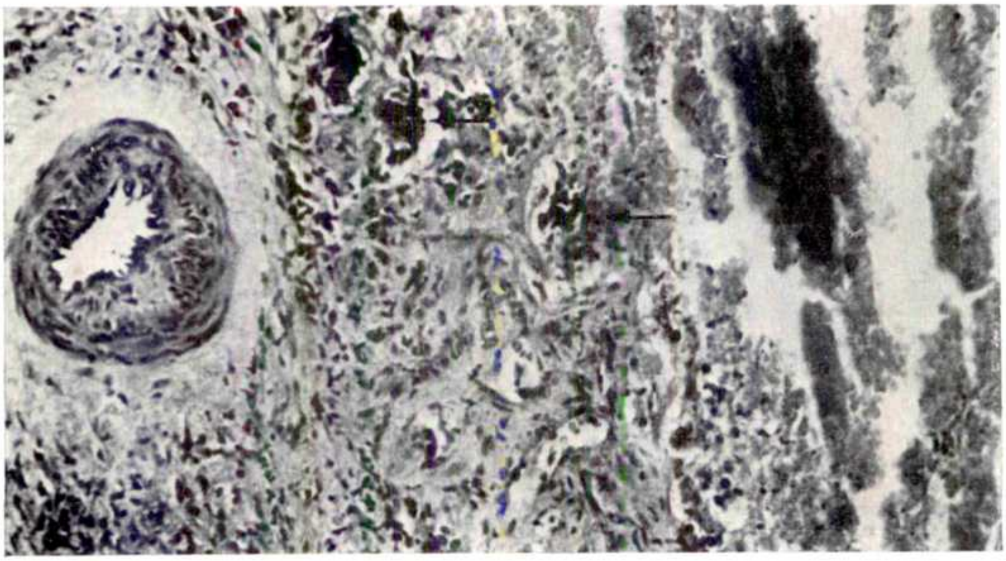


Fig. 6. Necrotic tumour on left with malignant cells in deep lymphatics. H & E. ×40.

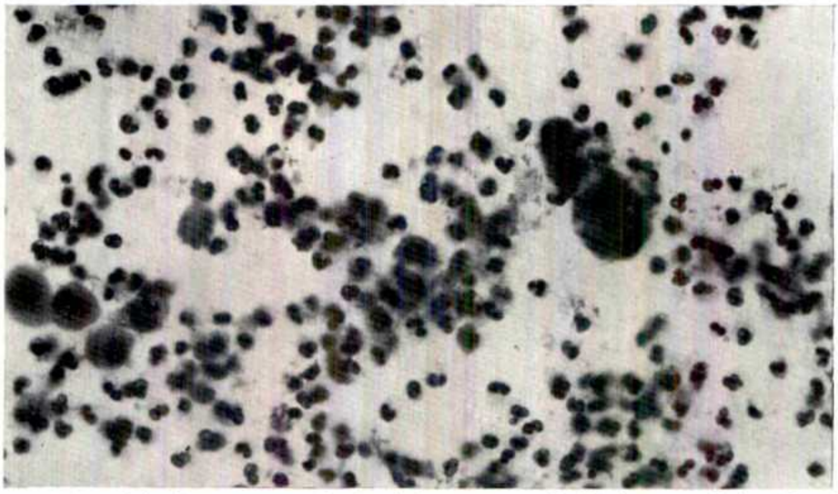


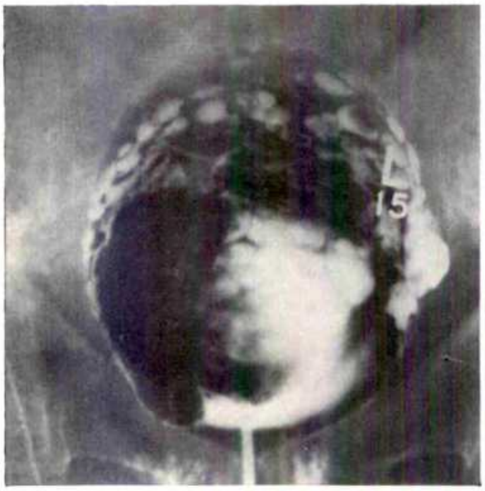
Fig. 7. Cytology—5 days following treatment showing inflammatory cells, histiocytes and altered malignant cells—Papanicolaou staining. ×40.

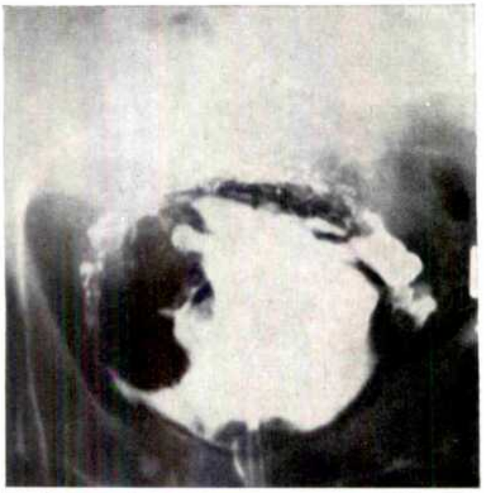
clear for a period of 9 months. Perurethral diathermy was usually sufficient to clear the bladder of tumour and the impression of this group is that the main mass of the tumour can be cleared with pressure therapy leaving only remnants to be treated in the conventional manner. In the 9 cases which correspond with the T_2 staging, further treatment in the shape of transurethral resections and/or radiotherapy had to be done within months of treatment. In 1 case, however, the treatment was repeated with apparently a good effect, the patient remaining clear of tumour for over a year. In the T_3 group, although some patients showed temporary improvement, all had to be treated by radiotherapy or further surgical procedures and, in fact, 4 of these group have subsequently died. In the remaining group, where treatment was known to be palliative only, all the patients died but symptomatically 4 out of 5 achieved great benefit.

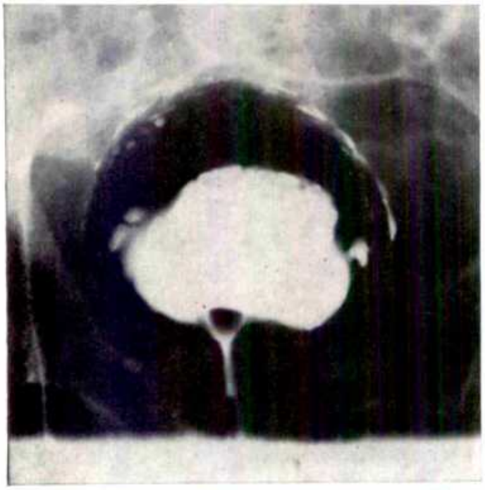
Relief of symptoms

T_1 Tumours. 9 patients in this group had all been referred with haematuria and 5 of them were also complaining of frequency and some dysuria. Following treatment, the haematuria ceased in all cases and they remained free of bleeding for 3 months following treatment. Frequency was relieved in all but 2 cases and, in fact, 7 out of the 9 were completely cleared of all urinary symptoms.

T_2 Tumours. Haematuria stopped in all 9 cases in this group, although in 2 patients who had had previous radiotherapy, minimal haematuria returned within 6 weeks due to a recurrence of the tumour. In both these, the haematuria had been severe enough to cause emergency admission to hospital and, in both cases, the bleeding was stopped following the pressure therapy. Frequency was marked in all patients in this group and in 8 out of the 9 the frequency was relieved by the therapy, with one exception, this patient being one who had had previous radiotherapy and was known to have a small contracted bladder which only allowed the balloon to be distended with 400 ml of sterile saline when the treatment was applied. Dysuria was completely relieved in the 5 cases that it was present. Following radiotherapy, or where there is a marked fibrosis of the bladder wall, one would not really expect to get a good response from treatment as the success of the treatment is almost certainly due to the ability of the bladder to stretch and to be stretched, leading to the occlusion of the blood vessels.







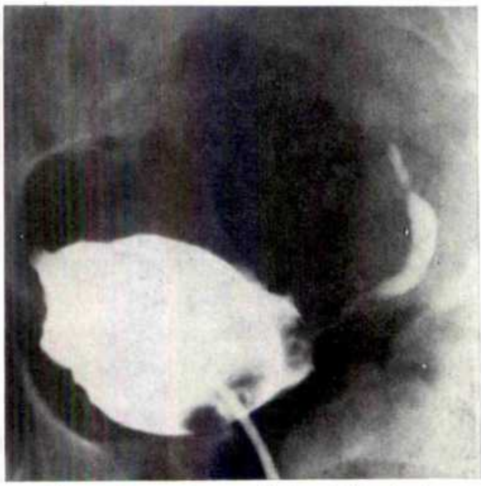


Fig. 8. Double contrast cystogram pre-treatment. **Fig. 9.** Double contrast cystogram 10 days following treatment. **Fig. 10.** Double contrast cystogram 3 months following treatment. **Fig. 11.** Double contrast cystogram showing reflux up left ureter after pressure therapy.

T_3 Tumours. In the 6 patients in this group haematuria was the predominant symptom, in 4 cases the haematuria being very heavy. The haematuria was vastly improved in all these patients, being stopped in 4 cases and much less in 2 others. Frequency was also relieved in 4 cases and dysuria completely relieved.

T_4 Tumours. All these patients complained of heavy haematuria and frequency. Bleeding was contained in 3 of the patients for several weeks and in the other 2 it was greatly reduced. Frequency and dysuria were relieved in 4 out of the 5 patients.

There is little doubt that the bladder pressure therapy does clear haematuria in most cases and in those where it tends to persist it is associated with very advanced malignant disease, and even in this group the patients' symptoms were greatly improved. Frequency was lessened in every case that it was present and dysuria was apparently minimised. There is no doubt that patients' symptoms are greatly relieved and this, of course, becomes particularly important in the advanced T_4 group.

Side-effects

There were no deaths or ruptured bladders following the 37 treatments. 1 patient developed a pulmonary embolus and had to be treated with anticoagulants. 4 other side-effects were noted as a direct result of the treatment.

(1) **Abdominal Pain.** 3 patients complained of severe low abdominal pain following treatment and developed the signs of peritonitis with lower abdominal tenderness and in 2 cases apparent rigidity. No rise in pulse rate or temperature was noted; they were sedated, and when reviewed, in 4 to 6 hours, their pains had eased and the rigidity had disappeared. The abdominal tenderness on palpation disappeared within 24 to 48 hours. One possible explanation for these symptoms may be the passage of either urine or saline passing from the balloon through the bladder wall into the peritoneal cavity.

(2) **Pyrexia.** 5 patients developed a temperature in the 48 hours following treatment. This did not appear to be related to a urinary tract infection, but they were treated with antibiotics and the pyrexia resolved in 3 to 4 days.

(3) **Urethral Stenosis.** 3 male patients developed marked stenosis of the distal urethra which caused difficulty in future cystoscopies. This stenosis was probably due to the instrumentation at the time of treatment.

(4) **Ureteric Reflux.** Ureteric reflux was noted quite accidentally on a post-treatment double contrast cystogram when an asymptomatic refluxing ureter was noted (Fig. 11).

Discussion

The treatment of bladder neoplasms using Helmstein's pressure method is a simple and safe method of treatment which can be repeated. This is particularly attractive in the elderly and frail in whom radical surgery or radiotherapy would be a major undertaking. Several patients in this series have fallen into this category. This is of importance in dealing with the advanced bladder growths where palliation is the only treatment that can be undertaken and where cessation of haematuria, diminution of frequency and dysuria in someone who is in the terminal stages of the disease is certainly a step forward in the treatment of bladder cancer. In the superficial group T_1 tumours there is no doubt that necrosis occurs consistently, the best results being obtained where the tumours were large and bulky. The recurrence rate is high over the next few months and so this therapy is of benefit only in reducing the bulk of the tumours which project into the bladder. It may be reasonably asked whether this pressure therapy can push malignant cells into the deeper layers via the lymphatics, but there would appear to be no way of answering this question. This may not occur much in the T_1 tumours, but there is no doubt that malignant disease can continue to flourish underneath necrosis in the T_2 and T_3 groups. Cystoscopically, the patient may have a good response to therapy but histologically it can be shown that the deeper layers are relatively untouched by the treatment and, therefore, this in itself is a contra-indication for this form of therapy being used in T_2 and T_3 tumours.

In this series, the results obtained by Helmstein (1972) have not been confirmed and there is no indication that advanced malignancy in the bladder is more sensitive than the more superficial and less malignant growths. Destruction of the large bulky T_1 tumours does, however, agree with the findings of England *et al.* (1973). There was no evidence of any damage to the intact bladder epithelium and, therefore, it is reasonable to assume that anoxic necrosis occurs as a direct result of the pressure stretching the blood vessels supplying the tumour. The findings in this series would agree with the supposition that the blood vessels in the inner layers of the bladder are more easily collapsed than those of the deeper muscle layers, and indeed this would confirm the different findings as obtained in this series between T_1 and the T_2/T_3 groups. There has been no evidence in this series to suggest necrosis of tumour cells in the lymphatics, and indeed demonstrable tumour in the lymphatics has been noted where there was apparently a good cystoscopic response to treatment (Fig. 6).

Conclusions

(1) This treatment is easily done, carries little risk and is very suitable in elderly unfit patients where more conventional means of therapy would be a serious hazard. (2) It is effective in stopping haematuria and in reducing frequency of micturition and dysuria. (3) This treatment reduces the bulk of T_1 tumours, particularly where these are large papillary-type growths. (4) It is not recommended in the treatment of T_2 and T_3 tumours. (5) It is an effective palliative therapy in advanced T_4 growths. (6) The treatment can be repeated without ill-effect.

Summary

30 patients with proven bladder malignant disease have been treated by Helmstein's hydrostatic pressure technique.

Massive necrosis of tumour tissue has been shown to occur at cystoscopy, cytologically and on histological examination.

Double contrast cystography can indicate reduction in tumour size within 2 weeks of treatment.

Haematuria is usually stopped with diminution of frequency and dysuria.

This treatment is suitable for large bulky T_1 tumours and advanced T_4 growths where palliation is the only treatment possible but not for T_2 and T_3 growths.

Elderly and ill patients can tolerate this therapy easily and there were no serious side-effects in this series.

I would like to thank Dr P. R. Brown, Consultant Anaesthetist, for giving the epidural anaesthetics throughout the series; the consultant pathologists and radiologists at the Huddersfield Royal Infirmary for their invaluable assistance; also the Medical Photography Department for help in the preparation of the photographs and illustrations.

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A Study of the Bladder Blood Flow During Distension in Rabbits

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Helmstein (1966, 1972) described a new method of treatment of bladder cancer by distending the urinary bladder to a pressure above the patient's diastolic blood pressure for several hours to produce necrosis of bladder tumour. Normal bladder mucosa is less easily affected by this distension.

It is not known why selective necrosis of the bladder tumour occurs but several theories have been postulated. The abnormal vessels in the terminal vascular bed of the tumour may collapse more easily when the intravesical pressure is increased, or the tumour cells could be more sensitive to anoxia than cells in the normal bladder mucosa. Finally, it has been suggested that tumour necrosis may be a result of an immunological process and Bubeník *et al.* (1970*a*, *b*) have found specific immunological reactions against bladder cancer cells in tissue culture.

The changes occurring in bladder blood flow during bladder distension have previously been recorded by Mehrotra (1953) who, using a transilluminating microscope, observed slowing of the blood flow in the vessels of the bladder wall of rats as the bladder pressure was increased.

The present study was undertaken to demonstrate the relationship between bladder distension and the blood flow through its wall.

Materials and Methods

Adult New Zealand white male rabbits of approximately 2 kg were studied.

Technetium-99m generators provided a supply of sterile technetium-99m as pertechnetate ion in isotonic saline solution ready for injection. Technetium-99m (^{99m}Tc) is a radioactive isotope which emits a 140keV gamma photon and has a half-life of 6 hours. The technetium generators were obtained from the Radiochemical Centre, Amersham, Bucks.

Lengths of 8 French gauge polythene tubing were used as urethral catheters.

A Cambridge multichannel recorder connected to the urethral catheter via a Devices strain gauge transducer was used to record the bladder pressures.

The radioactivity was measured with a scintillation counter, shielded with lead except for one face, and was connected to a recording ratemeter.

Anaesthesia was achieved in every animal by intravenous administration, via an ear vein, of sodium pentobarbitone (veterinary Nembutal). A dose of 60 mg of Nembutal to induce anaesthesia and 15 mg increments to maintain anaesthesia during the procedure were given.

A small midline abdominal incision was made to expose the bladder. The catheter was passed along the urethra into the bladder and connected to the recorder via the transducer to measure the bladder pressure in millimetres of mercury. A silk ligature was then applied around the penis to prevent leakage along the urethra during distension. The bladder was distended to the required pressure by running normal saline through the catheter into the bladder. The bladder blood flow was measured indirectly by observing the rate of clearance of a radio-isotope (technetium-99m) from the bladder wall. The technetium-99m was drawn up into a 1 ml tuberculin syringe and 0·02 ml was injected into the bladder wall with a fine needle (27 gauge) at a constant site (Fig. 1). The level of activity was immediately measured by the scintillation counter which was placed over the bladder with its face 2 cm from the bladder surface, the counter being connected to the recording ratemeter to give a continuous record of the

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rate of clearance of the radio-isotope. The procedure was carried out with the bladder flaccid and distended to various pressures from the 10 mm Hg to 80 mm Hg and finally in decompressed bladders after distension. 10 animals in each pressure group were studied. At the end of these procedures the wounds were closed, the silk ligature around the penis divided, the urethral catheter removed and the rabbits allowed to recover.

Results

The clearance of the radio-isotope technetium-99m (^{99m}Tc) followed a simple exponential curve. The clearance was reduced with increasing bladder pressures (Figs. 2-4). When these curves were plotted on to semilogarithmic graph paper straight lines were obtained (Figs. 5-7). The slope of this line (clearance constant λ) is a quantitative measure of the total ability of the bladder circulation to remove and also to supply freely diffusible substances. This slope (λ) was therefore recorded and used as a summary index of the rate of blood flow through the bladder. The blood flow through the bladder is reduced to half that of a resting bladder when the bladder is distended to 20 mm Hg, reduced to a quarter at a bladder pressure of 40 mm Hg and reduced to 1/20th when the bladder pressure is raised to 80 mm Hg.

The variability of the slopes decreased as the bladder pressure was increased and this is significant (Table I). This can be explained by the fact that the resting bladder pressure varied from 2 mm Hg to 8 mm Hg and this would account for the increased variability of the slopes in this group.

In order to apply an analysis of variance technique the data were transformed to remove this heterogeneity. The logarithm of each slope was taken (Table II) and this proved successful in attaining homogeneity of variance and also produced a nearly linear relationship of log λ (bladder blood flow) with bladder pressure.

Regression analysis incorporated in analysis of variance showed that there were great differences in blood flow at different pressures and that most of this difference could be explained by a simple linear relationship between log λ (slope) and bladder pressure:

Table I

The Variability of Slopes Within each Group

Pressure mm Hg	Resting 0-8	10	15	20	25	30	40	50	60	80
Mean slope	1·87	1·09	0·78	0·67	0·61	0·61	0·48	0·32	0·27	0·09
Variance	0·2337	0·0832	0·0045	0·0090	0·0088	0·0086	0·0033	0·0051	0·0034	0·0013

Table II

The Variability of the Log of the Slopes in each Group

Pressure mm Hg	Resting	10	15	20	25	30	40	50	60	80
Log Mean Slope	0·60	0·05	−0·25	−0·41	−0·50	−0·53	−0·73	−1·16	−1·33	−2·51
Variance	0·064	0·065	0·007	0·021	0·026	0·074	0·013	0·061	0·045	0·138

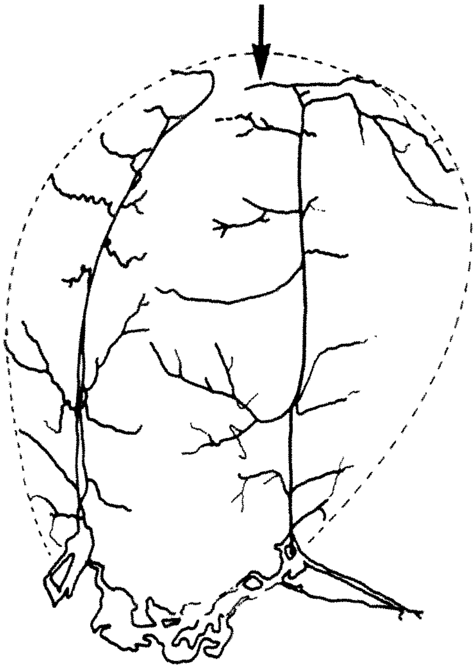


Fig. 1. Diagrammatic representation of the gross vascular pattern of the rabbit's bladder to show the site where the technetium-99m was injected.

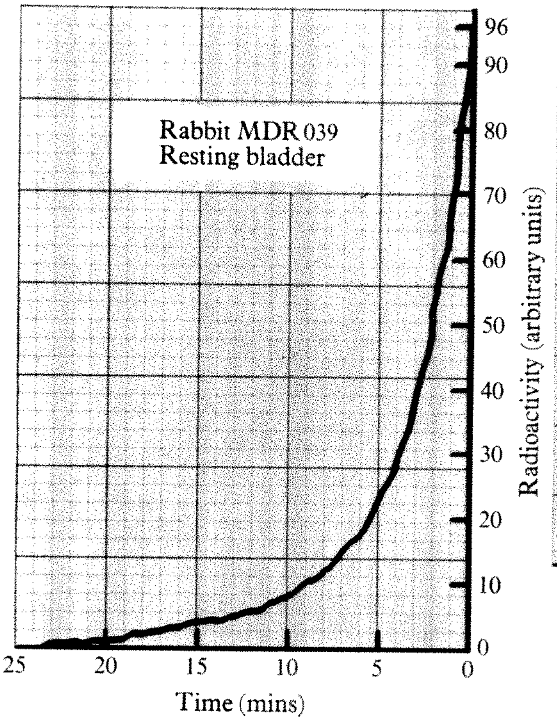


Fig. 2. Clearance of technetium-99m in a resting bladder.

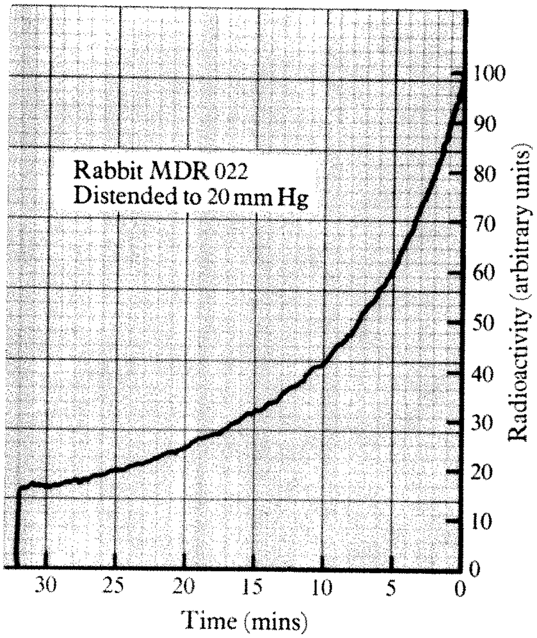


Fig. 3. Clearance of technetium-99m in a bladder distended to 20 mm Hg.

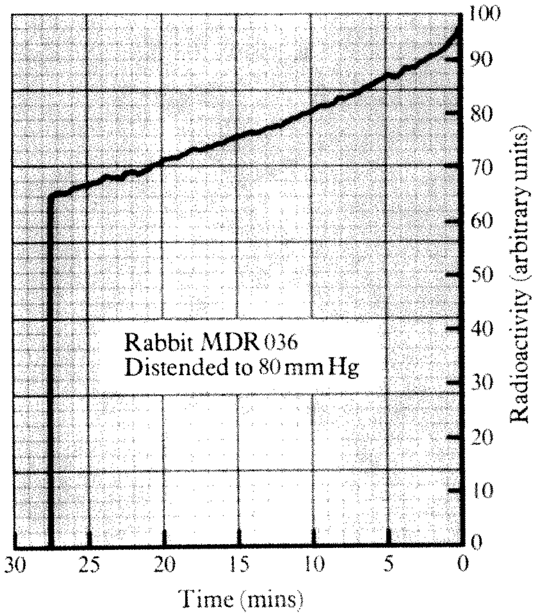
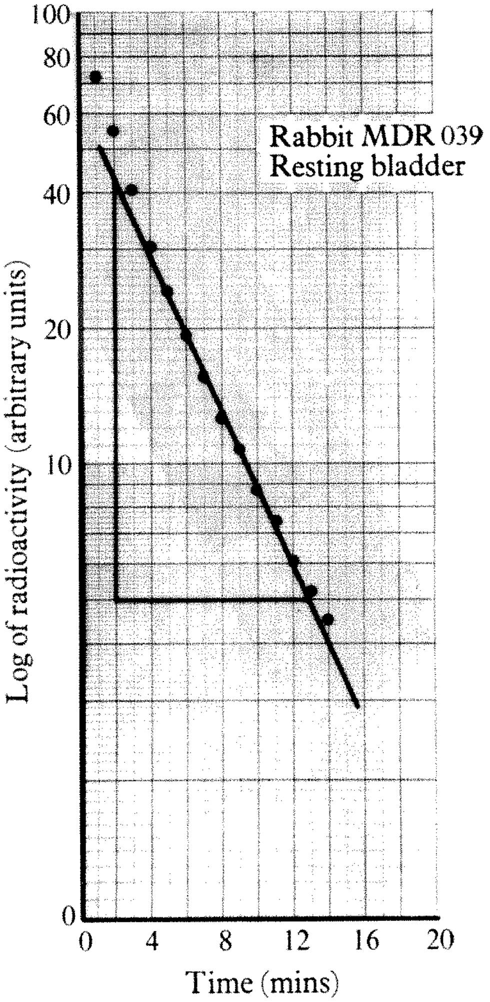


Fig. 4. Clearance of technetium-99m in a bladder distended to 80 mm Hg.

Fig. 5. Clearance curve, plotted on to semi-log paper, of a resting bladder.



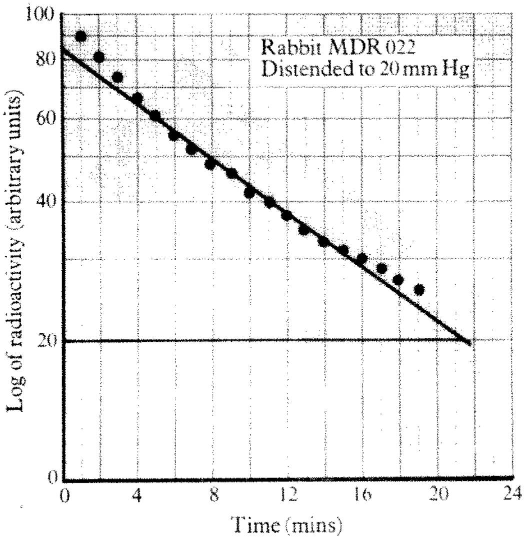


Fig. 6. Clearance curve, plotted on to semi-log paper, of a bladder distended to 20 mm Hg.

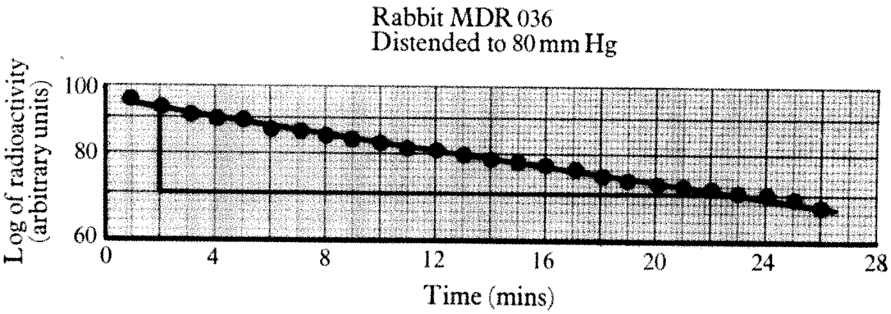


Fig. 7. Clearance curve, plotted on to semi-log paper, of a bladder distended to 80 mm Hg.

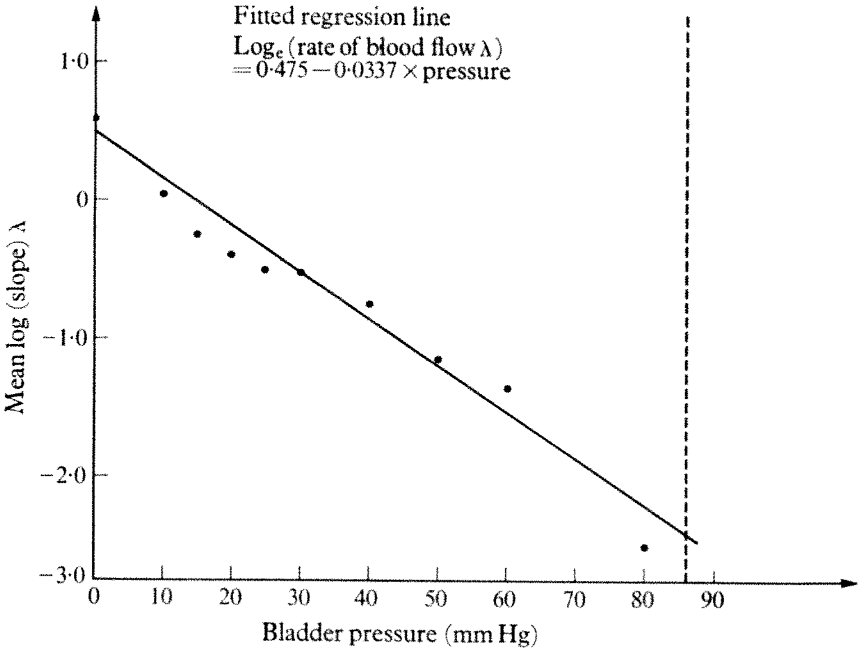


Fig. 8. Fitted regression line demonstrating relationship between bladder pressure and bladder flow.

Log$_e$ (rate of blood flow) $= 0{\cdot}475 - (0{\cdot}0337 \times$ bladder pressure) (Fig. 8). The over-all picture is that of a strong and precise linear relationship with pressure effecting a proportional reduction in the rate of blood flow from the bladder.

Discussion

Where the tissue uptake of a substance is measurable by the use of radioactive isotopes, it may be possible to estimate blood flow without resorting to blood sampling. On this basis, measurement of peripheral blood flow, was proposed by Smith and Morales (1944), using radioactive krypton and by Smith and Quimby (1945) using radioactive sodium. These methods of measuring regional blood flow following intravenous injection of a radio-isotope have many disadvantages such as complex mathematical analysis, exposing the entire body to radiation, of requiring at least 30 minutes for a single measurement, and of being incapable of demonstrating rapid serial changes in blood flow.

Kety (1949) suggested that the diffusible tracer substance should be introduced directly into the tissue being studied and that its clearance from the tissue would be a measure of the local tissue circulation.

Schnur, Simons and Tauxe (1969) used technetium-99m to study the vascular status of pedicle skin flaps and compared it with radio-isotopes of sodium, (^{23}Na) potassium, (^{42}K) and iodine (^{131}I) and attained more or less identical clearance rates. Repeated injections of ^{99m}Tc at the same site under identical environmental conditions showed excellent reproducibility in clearance rates (Tauxe *et al.*, 1970). These workers preferred ^{99m}Tc pertechnetate because of its relatively short half-life, low radiation, high counting efficiency and simplicity of the instrumentation necessary for counting.

This method, using the radio-isotope technetium-99m, therefore offered a convenient means of measuring bladder blood flow.

Summary

This study has shown that there is a linear relationship between bladder blood flow and bladder pressure. At a bladder pressure of 80 mm Hg (blood pressure in rabbits varying from 90/60-100/70 mm Hg) the blood flow in the bladder is minimal.

It is suggested that bladder distension at 80 mm Hg in rabbits leads to hypoxia in the bladder wall as a result of the reduced blood flow.

Prolonged bladder wall hypoxia occurring as a result of prolonged bladder distension may be responsible for selective necrosis of bladder tumours.

I would like to thank Mr J. C. Smith for his help and encouragement in the preparation of this paper. I am indebted to Miss Jenny Brennan for carrying out the statistical studies and to the Department of Medical Illustration for the preparation of the photographs and figures. I am very grateful to Mrs Jean Broadis for her patience and kindness in the typing of this manuscript.

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Is Urography Necessary for Patients with Acute Retention of Urine Before Prostatectomy?

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In recent years it has been customary in this, as in other urological units, to insist upon an excretion urogram before carrying out a prostatectomy. In the routine outpatient, there is little room for argument as to the wisdom of this investigation, but in the patient admitted with acute retention of urine, to insist upon an excretion urogram necessitates a certain delay between admission and operation. Is this delay justified by the value of the information which the urogram provides? We thought it was time to try to answer this question.

Material and Methods

203 patients were admitted to the London Hospital from 1967 to 1973 as emergencies with acute or acute-on-chronic retention of urine. (Other patients who developed retention while already in hospital for some other condition were excluded from this study.) In 49 of these men a urogram had been done shortly before admission—many of these were already on the waiting list for prostatectomy—and in another 23 patients the urogram was considered unnecessary. In 126 men the operation on the prostate was postponed until a urogram had been done. 5 other patients resumed satisfactory micturition and the operation was not thought to be necessary at this admission (Table I).

Radiographic Abnormalities in Men with Acute Retention

180 urograms were available on 203 patients: 38 abnormalities were noted in 35 urograms (Table II) but in most instances, the abnormalities consisted of upper tract obstruction—hydroureter or hydronephrosis, or, in 3 cases, non-function or poor function of one or other kidney.

4 patients were found to have diverticula. One was found to have a vesical calculus, but this finding was made at preliminary cystoscopy, since the urogram had not been done. One instance each of renal cyst, calculi, and duplex kidney were found.

Table I

IVP in Acute Retention
(Total Number of patients 203)

	Operation	No operation
IVP during admission	126 (62·1%)	5 (2·4%)
No IVP during admission	72 (35·5%)	0

Table II

Abnormalities Found in 180 IVPs

Abnormality	No.	%
Hydronephrosis:		
Unilateral	14	38·8
Bilateral	11	26·9
Diverticula	4	10·5
Filling defect (? tumour)	3	8·0
Poorly excreting kidney	2	5·4
Non excreting kidney	1	2·6
Duplex collecting system	1	2·6
Renal stone	1	2·6
Renal cyst	1	2·6
Total	38	

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

Table III

Abnormalities Associated with Elevated Blood Urea

	No. of patients	No. of abnormalities	% of total
Blood urea < 50 mg/%	143	19	13·3
Blood urea > 50 mg/%	37	16	43·2
	$P<0{\cdot}002$		

	No. of patients	Hydronephrotic changes excluded	% of total
Blood urea < 50 mg/%	143	8	5·5
Blood urea > 50 mg/%	37	5	13·5
	$P>0{\cdot}05$		

As one might expect, hydroureter and hydronephrosis were found more commonly in men with a raised blood urea (Table III) but apart from this, the other abnormalities were no more common in those with a raised blood urea than in those with normal levels.

Length of stay in Hospital

The mean preoperative stay in hospital of men who did not have to wait for a urogram was 4·2 days: if they waited for a urogram to be done it was 7·9 days ($P<0{\cdot}001$, Table IV). Similarly, the total hospital stay was longer (19·7 days) in men waiting for urography than in those who did not have it done at this admission (16·5 days, Table V). Since our method of dealing with patients admitted with uraemia is to drain the bladder over a few days while the electrolyte deficiency, acidosis and anaemia is corrected, it was important to be sure that the additional stay in the urogram group was not related to a preponderance of uraemic patients: there was no significant difference (29/126 compared with 16/72, see Table VI). Nor was there an increased incidence of infection in the group submitted to urography (Table VII), or any difference in the kind of operation which was performed (Table VIII). The same proportion in each group underwent open operation and transurethral resection.

Discussion

The incidence of the abnormalities detected in the urograms which were done in these patients is similar (19·4%) to that as reported recently by Boerema (1972) in patients prior to prostatectomy, but two-thirds of the abnormalities consisted of features of upper tract obstruction, and although these were sometimes very severe, they did not of themselves influence either the decision to operate, or the type of operation which was done. These decisions were based upon the metabolic state of the patient and his general condition. In respect of the management of the patient with acute retention these findings were therefore irrelevant.

What would be of more relevance would be to discover that preliminary urography had diagnosed diverticula, stones, or carcinoma sufficiently often and accurately to allow the surgeon to plan treatment ahead of cystoscopy. In the event, although 4 diverticula were found, only 1 was large enough to warrant operation. This incidence of diverticula (2·2%) is little different from that found by Badenoch (1965) as a coincidental finding in a series of 3,068 urograms. In

Table IV

Days in Hospital Prior to Operation

	No. of patients	Mean time in days before opn.
No IVP preopn.	72	4·2
IVP preopn.	126	7·9
	$P < 0{\cdot}01$	

No. of patients	Admission to IVP (Mean time in days)	IVP to opn. (Mean time in days)
126	3·5	4·4

Table V

Total Hospital Stay

	No. of patients	Hospital stay (Mean time in days)
No IVP preopn.	72	16·5
IVP preopn.	126	19·7
	$P < 0{\cdot}05$	

Table VI

Uraemia

	No. of patients	No. with elevated urea	% of total
No IVP preopn.	72	16	22·2
IVP preopn.	126	29	23·0
	$P > 0{\cdot}05$		

any case, these diverticula would have been found at preliminary cystoscopy, and if the surgeon were in doubt as to their extent, it would be possible to postpone a decision pending more complete investigation by cystography. No vesical stones were found on radiography in this series, and in any case, they would have been found at cystoscopy, as was illustrated by one case reported above, or perhaps revealed in a preliminary plain radiograph of the urinary tract without having recourse to urography. As for carcinoma of the bladder, the excretion urogram is notoriously unreliable as a means of detecting a tumour in the bladder: all 3 suspicious filling defects noted in these urograms turned out not to show tumour on cystoscopy. The renal cyst, the case with renal calculi, and the duplex kidney which were the remaining abnormalities shown in these urograms did not call for any special alteration in treatment, nor was their incidence any more common than one would expect to find as an incidental finding in a large series of autopsies (Heptinstall, 1966; Allen, 1962).

What was the price of insisting on this rather unrewarding investigation? True, the risk of the urogram is very small (perhaps a mortality of 1 : 50,000 and a severe reaction rate a little greater than this; Fischer and Doust, 1972) but the delay which was necessitated by waiting for the urogram is a more important consideration. The patient whose operation was put off for the urogram had to wait more than 3 days longer in hospital. Insistence upon preoperative urography led to 126 patients spending 446 days more in hospital.

Not only is this delay costly, in terms of the cost of hospital accommodation, but every extra day during which the patient must use a catheter adds to the risk of acquiring urinary infection.

These findings suggest that there is no real reason for insisting upon a preliminary urogram in the patient who comes to hospital with acute retention. There may of course be other indications for insisting upon the excretion urogram: these could be evaluated on their merits. Perhaps there is a case for carrying out a plain radiograph of the urinary tract to reveal renal or vesical calculi. What does emerge from this study is, once more, the overriding importance of a careful preliminary cystoscopy in every patient about to undergo prostatectomy.

Table VII

Operation and Infection

No preopn. IVP	No. of patients	Days prior to opn. (mean)
Not infected	60	4·23
Infected	12	4·17

$P > 0{\cdot}05$

Pre-opn. IVP	No. of patients	Days prior to opn. (mean)
Not infected	110	7·73
Infected	16	9·0

$P > 0{\cdot}05$

Table VIII

Method of Treatment

	No. of patients	Mean length of stay postoperatively (days)
TUR	143	11·5
Open operation	55	14·5

$P < 0{\cdot}01$

	No. treated by TUR	No. treated by open operation
IVP preopn.	54	18
No IVP preopn.	89	37

$P > 0{\cdot}05$

Summary

In 180 urograms performed on 203 patients admitted to hospital with acute or acute-on-chronic retention of urine 38 abnormalities were noted, most of them being related to upper tract obstruction.

Of 4 diverticula detected only one needed treatment.

Waiting for the urogram imposed an extra delay of more than 3 days between admission and operation and an equal prolongation of the whole hospital stay.

There appears to be no justification for routine urography prior to prostatectomy in the patient admitted with urinary retention.

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Identification of a Prostate in Female *Praomys (Mastomys) Natalensis* using ^{3}H steroids

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Small periurethral glands in some female mammals have been considered as the homologue of either part or the whole of the male prostate. It has also been reported that there are rudimentary prostates in some female rats, mice and the proportion of animals in which this occurs varies within the different strains (Korenchevsky, 1937; Price, 1939). In the human, the ducts and glands surrounding the female urethra have been regarded as a "prostate" (Moore, 1960) but their responsiveness to hormones is unknown.

A well-developed prostate was described in all female *Praomys* (*Mastomys*) *Natalensis* by Brambell and Davis (1940). This prostate consists of two lobes lying posterior to and on each side of the bladder neck. Dorsally, these lobes are separated by the urethra and vagina, and therefore this anatomical arrangement resembles the ventral lobes of the male *Mastomys* (Fig. 1). The histological appearances also closely resemble the ventral lobes of the female (Fig. 2, A and B). The organ weight and the activity of acinar cells fluctuate with the oestrous cycle, being highest during the luteal phase (Brambell and Davis, 1940).

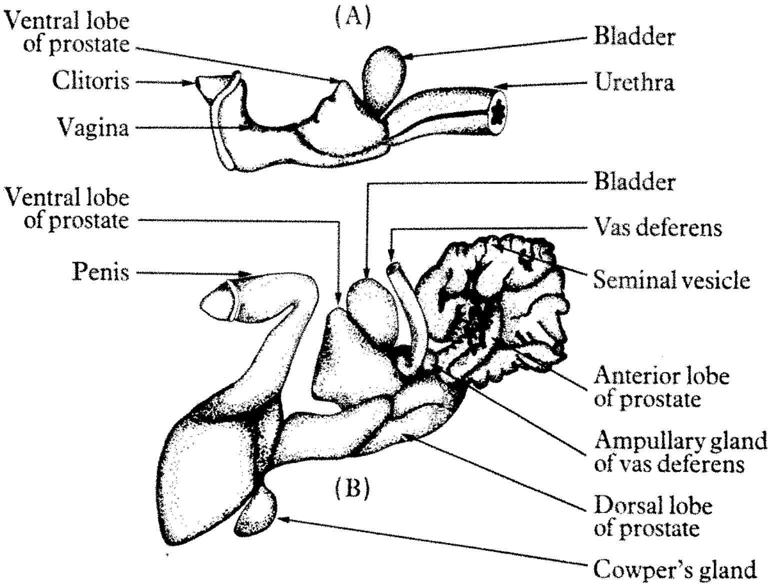

Fig. 1. Dissection of the reproductive organs of the female (A) and male (B). (Adapted from Brambell and Davis, 1940).

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

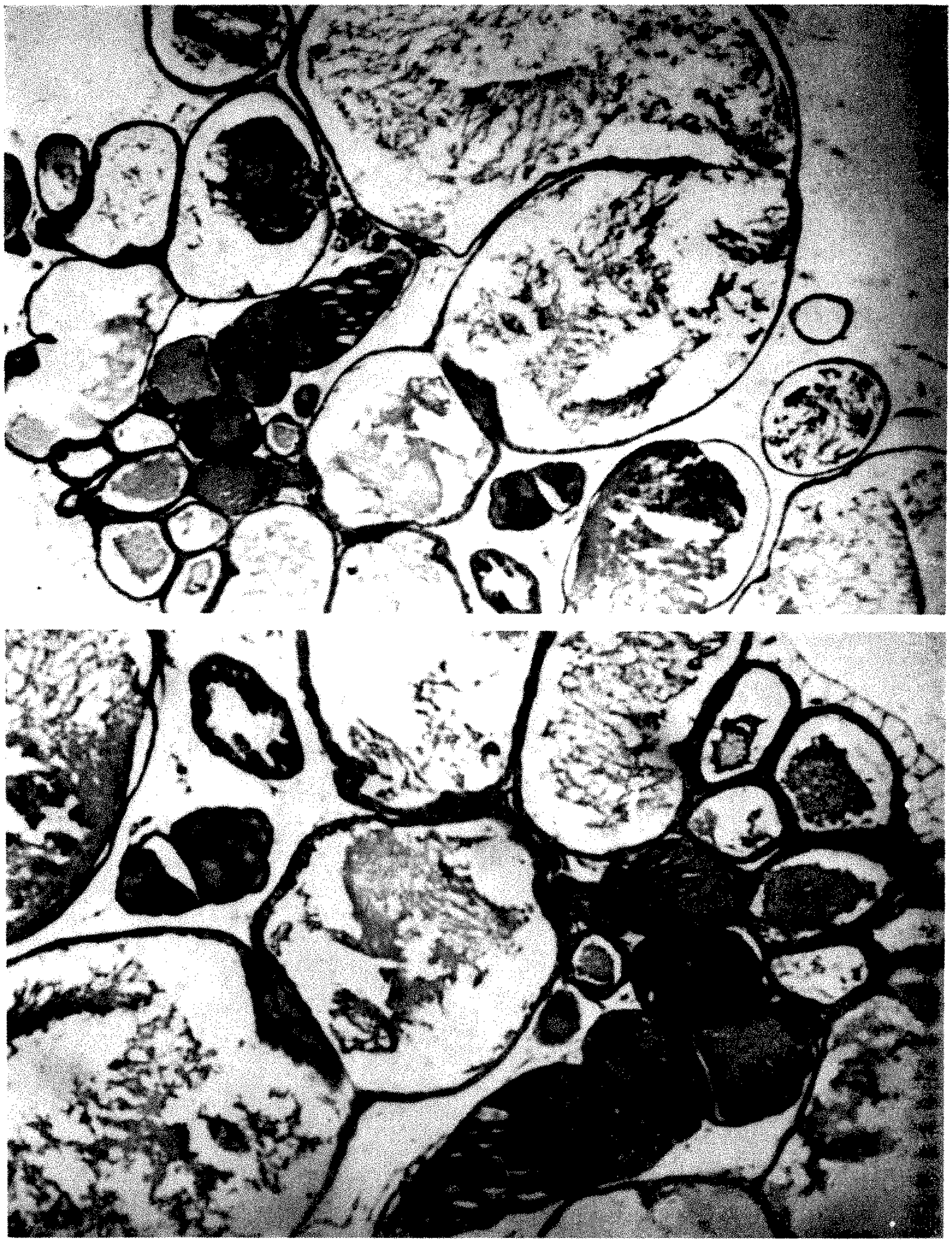

Fig. 2.A, B. Histological sections of ventral lobes of female (A) and male (B) both composed of acini lined by a flattened epithelium and containing amorphous eosinophilic coagulum; the histological appearances of male and female are identical.

Hyperplasia and adenocarcinoma have been reported in the prostate of some older female *Mastomys* (Snell and Stewart, 1965). Proliferative changes have been found to occur with increasing age and hyperplasia has been induced experimentally (Holland, 1970). These interesting observations have raised the possibility that this female prostate might be used as a model for the study of prostatic hyperplasia as well as adenocarcinoma. However, it is not yet known whether this female prostate is androgen dependent, and if it is so, is the dependency similar to that seen in the male *Mastomys*?

Materials and Method

Praomys (*Mastomys*) *Natalensis* were bred in our colony and 4-month-old females were used in this study.

[1,2,6,7-^{3}H] testosterone (specific activity 100 Ci/m mol, purity above 98%) and [2,4,6,7-^{3}H] oestradiol 17β (specific activity 100 Ci/m mol, purity above 99%) were obtained from the Radiochemical Centre, Amersham. Solutions of these steroids were made in 20% ethanol/saline. Scintillation fluid was prepared by dissolving 4 g PPO (2·2 diphenyloxazol) and 0·1 g POPOP (1,4-bis-2-(5-phenyloxazolyl)-benzene) (Koch-Light Laboratories Ltd.), in 1000 ml toluene AR (BDH).

Mastomys were injected intramuscularly with either labelled testosterone or oestradiol in a dose of 100 μCi/100 g body weight. They were then sacrificed at 2 or 16 hours after injection. Prostate and pieces of uterus, ovary, fallopian tubes, vagina, liver, kidney and diaphragm were dissected out, and weighed on a Torsion balance. Each tissue sample was placed in a scintillation vial, and 0·5 ml of Soluene 350 (Packard) was added. After the tissue had been digested during overnight incubation at room temperature, 10 ml of scintillation fluid was added to each vial and the radioactivity was counted in a scintillation spectrometer. Quenching was corrected by the internal standard method using [^{3}H] testosterone. The results were expressed as disintegrations per minute per mg of tissue.

Results

The results showed that 2 hours after injection the uptake of [^{3}H] testosterone by prostate was less than liver and kidney, but higher than other target or non-target tissues. However, liver and kidney which had accumulated more radioactive testosterone than prostate lost most of labelled testosterone after 16 hours. In contrast, at 16 hours, the prostate had retained more [^{3}H] testosterone than any other target or non-target tissue (Fig. 3). Similar results have also been shown in the prostate of male *Mastomys* (Ghanadian, Holland and Chisholm, 1974).

The comparison of the uptake of [^{3}H] oestradiol with that of [^{3}H] testosterone by the urogenital tract of the female *Mastomys* is shown in Table I. The uptake of [^{3}H] oestradiol by the prostate was significantly less than the uptake by the uterus, ovary, fallopian tubes and vagina. However, there was a greater uptake of [^{3}H] oestradiol by the female prostate compared to non-target tissues such as diaphragm.

In order to investigate whether or not unlabelled testosterone could suppress the uptake of labelled testosterone, a 100 μg of unlabelled testosterone was injected prior to the injection of labelled testosterone. The results demonstrated that there was a significant suppression in the uptake of testosterone by the prostatic tissue ($P < 0{\cdot}001$), whereas the uptake of [^{3}H] testosterone by other tissues of the female *Mastomys* did not change significantly (Table II).

Discussion

Although the histological appearance and anatomical location of the female prostate in *Mastomys* closely resembles the male prostate, the responses by this tissue to androgens and oestrogens have not been fully investigated. The first step in the interaction of a hormone with its target tissue is by

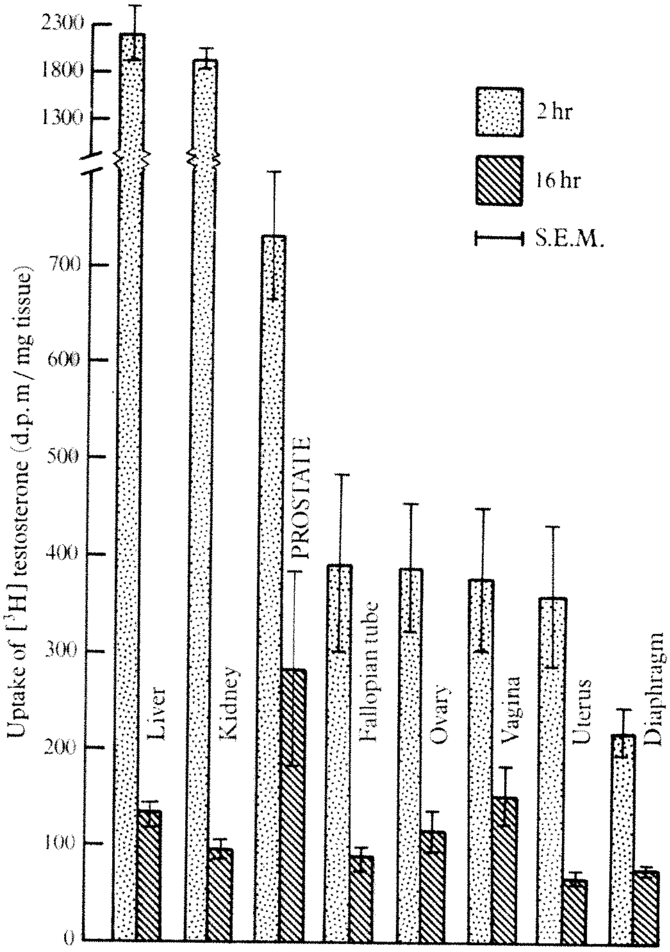

Fig. 3. *In vivo* uptake of [³H] testosterone by various tissues of female *Mastomys* at 2 and 16 hours after injection.

direct uptake of that hormone. Therefore, the uptake of androgens and oestrogens by the female prostate was used to identify whether or not this tissue resembled the male prostate.

The results reported in this paper suggest that the ability of the prostate to take up and to retain testosterone differs from either target or non-target tissues of the female *Mastomys*. This prostate also showed the ability to retain radioactive testosterone as long as 16 hours after injection, and the concentration of this hormone was significantly higher than the other tissues. This is in accordance with findings in the prostate of the male rat (Tveter and Attramadal, 1968) and male *Mastomys* (Ghanadian *et al.*, 1974).

The uptake of [³H] oestradiol by the prostate appeared to be less than the uptake by uterus, ovary, fallopian tubes and vagina, but higher than non-target tissues, such as the diaphragm. This is in agreement with the finding that the prostate in male *Mastomys* (Ghanadian *et al.*, 1974) and rat (Tveter, 1970; Ghanadian and Fotherby, 1972) are also able to take up more oestradiol than non-target tissues.

The competition between labelled and unlabelled testosterone for the androgen binding sites and, therefore, the significant decrease of the uptake of radioactive testosterone due to the injec-

Table I

In vivo Uptake of [^{3}H] Testosterone and [^{3}H] Oestradiol by Various Tissues of Female *Mastomys* 2 hours after Injection of Labelled Steroids. Values are Mean ±SEM expressed as d.p.m./mg of Tissue

	[^{3}H] Oestradiol	[^{3}H] Testosterone
Uterus	3416·6±344·40	360·8± 74·20
Ovary	2039·5±614·30	388·6± 67·50
Fallopian tubes	2347·4±344·51	391·3± 94·61
Vagina	1894·8±514·40	379·2± 75·89
Prostate	680·9±104·06	733·0± 65·80
Liver	1488·4±486·44	2223·6±279·20
Kidney	1153·7±316·85	1919·9± 36·60
Diaphragm	294·8± 59·70	218·0± 23·97

Table II

Effect of Unlabelled Testosterone on the Uptake of [^{3}H] Testosterone by Various Tissues of Female *Mastomys*. Values are Mean ±SEM expressed as d.p.m./mg of Tissue. Each Animal received 100 μCi/100 g Body Weight of [^{3}H] Testosterone

	[^{3}H] Testosterone	[^{3}H] Testosterone + 100 μg Testosterone	Significance (Value for P)
Prostate	733·00± 65·80	244·20± 29·50	<0·001
Uterus	360·65± 74·20	304·60± 31·70	>0·1
Ovary	388·65± 67·70	214·00± 52·73	>0·1
Fallopian tubes	391·30± 94·61	249·00± 20·85	>0·1
Vagina	397·23± 75·89	273·85± 26·45	>0·1
Liver	2223·67±279·20	2054·76±675·29	>0·1
Kidney	1919·90± 36·60	2067·43±761·08	>0·1
Diaphragm	218·09± 23·97	201·50± 17·00	>0·1

tion of unlabelled testosterone, is also similar to the prostate of the male rat (Tveter and Attramadal, 1968; Ghanadian and Fotherby, 1970).

These observations demonstrate that the androgen uptake by the prostate of the female *Mastomys* is identical to that of the male. Thus, this female prostate provides an opportunity for experiments related to prostatic research to be carried out in a low androgen milieu: for example, this would permit the study of drug effects on the prostate to be made without interference from high endogenous androgens.

The standard method for depriving prostatic tissue of endogenous androgens is by castration, but during the period after castration the protein receptors for androgens are affected (Baulieu and Robel, 1970) and there is also a significant shrinking of the prostate. Therefore, the present model would appear to offer many advantages for studying factors influencing the functional activity of the prostate; it may also prove to be a suitable model for studying prostatic cancer.

Summary

The female of the species *Praomys (Mastomys) Natalensis* has a ventral prostate similar both in position and in histological appearance to the ventral lobe of the male prostate. The hormonal uptake of this female prostate has been investigated using [^{3}H] testosterone and [^{3}H] oestradiol.

The results showed that the uptake of these steroid hormones by the prostate was identical to our findings in the male prostate.

The potential value of a female prostate in prostatic research is discussed.

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The Technique and Results of One-stage Island Patch Urethroplasty

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Over the last 10 years we have performed 205 urethroplasties of various types for strictures which were not amenable to conventional treatment by intermittent dilatation, or which were complicated by fistulae or post-dilatation bacteraemia. Most of these strictures have involved the posterior urethra (Table I) so that most of our experience has been with the ∩-shaped scrotal flap urethroplasty, or one of its several modifications (Blandy *et al.* 1968, 1971, 1972, 1974; Symes and Blandy 1973). One of the principal drawbacks of this type of urethroplasty is that the patient must undergo two operations separated by an interval of several months between first and second stages.

Table I

205 Urethroplasties. Site of Stricture

			%
Meatus	21		10·2
Penile	15		7·3
Posterior	130	169	82·5
Full length	39		
	205		100·0

Leadbetter and Leadbetter (1962) referred to a method of letting in an island of skin based on a pedicle of dartos muscle as a means of treating penile strictures in children in one stage. This technique received little attention until it was described again by Orandi (1968, 1972). Following Orandi's publication, we tried this method for a few anterior urethral strictures and were pleased with its simplicity and its good results. Unfortunately anterior strictures were seldom encountered which could not be dealt with perfectly well by intermittent dilatation, and our major clinical problem continued to be the difficult high posterior bulbar and membranous urethral strictures. Orandi's pedicled island of skin could not be made to reach high up into the posterior urethra.

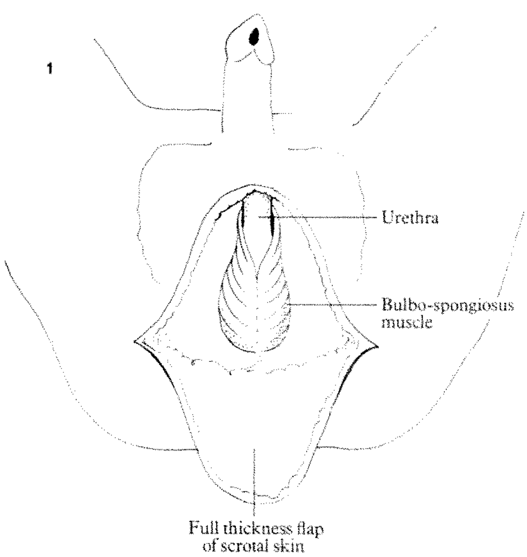
By now our experience with the ∩-shaped scrotal flap had made us confident of its excellent blood supply and ready adaptability. Perhaps, it seemed, we could make an island on a pedicle of the dartos obtained from the tip of the scrotal flap. Our first patient presented 3 years ago: since then we have come to employ this one-stage technique increasingly often.

Method

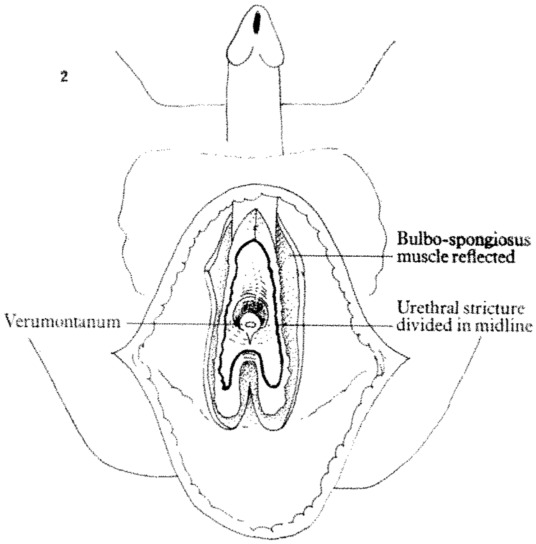
The operation begins by forming a ∩-shaped scrotal flap which is based upon a wide base, and is carried well posteriorly so that the edge of each incision almost reaches the ischial tuberosities.

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

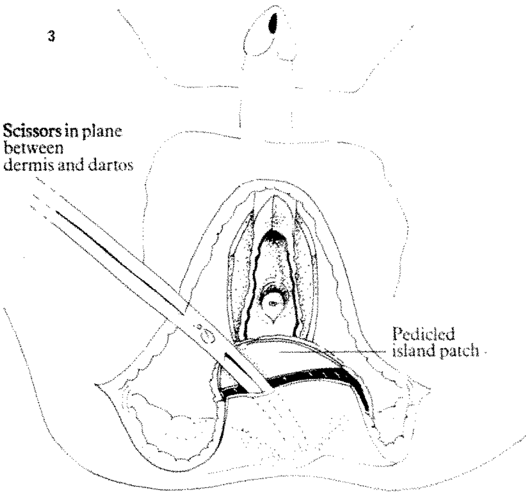
1



2


Bulbo-spongiosus muscle reflected
Verumontanum
Urethral stricture divided in midline

3



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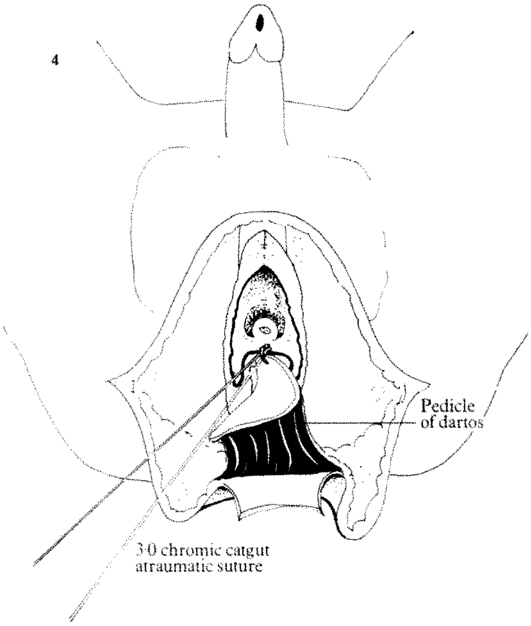

Fig. 1. The ∩-shaped scrotal flap.

Fig. 2. The urethral structure divided.

Fig. 3. The plane between the dermis and dartos.

Fig. 4. Fixing the apex to the flow of the urethra.

Unless the flap is carried well back, it is difficult to get a clear view of the deeper part of the urethra (Fig. 1).

At first the flap is carried through the full thickness of skin and dartos and allowed to fall back. This allows the surgeon to keep open the option of making a one- or a two-stage operation according to the findings in the urethra. If, for example, he encounters many false passages or fistulae, he may think it better to perform the procedure in the standard 2 stages.

After reflecting the bulbospongiosus muscle, the urethra is slit open along its ventral midline, and this incision is carried right through the full length of the stricture. Not only must the narrow segment of the corpus spongiosum be laid open, but any periurethral fibrous bands must also be severed completely. At the end of this step in the operation one must be able to feel the verumontanum easily, and feel no bands or ridges of fibrous tissue behind the urethra (Fig. 2).

Now the decision must be taken whether or not to try to complete the urethroplasty in one stage. If it is not a very complicated stricture, then nowadays we prefer to go ahead with a one-stage patch. The island of skin is formed by taking an ellipse from the tip of the scrotal flap. The knife divides the dermis down to, but not through, the dartos. The plane of cleavage between the dermis and the dartos is then opened up with curved scissors (Fig. 3) until the island patch has been provided with a sufficiently long and supple pedicle to allow it to be placed in the urethra without the least tension.

Trimming off the sharp ends of the ellipse of skin, one end is now sewn into the apex of the incision in the floor of the urethra. This is the only difficult part of the operation (Fig. 4). We find it most convenient to use 3-0 chromic catgut on a small half-circle atraumatic needle. With a little practice it is not difficult to manipulate the needle in the posterior urethra, and once the suture has been placed and tied, the insertion of the remaining stitches becomes progressively more easy, since it is now possible to pull down the edge of the urethra by traction on the suture.

The patch is sewn in with one layer of continuous catgut. As the incision in the urethra is patched, it becomes necessary to trim away surplus skin, for we have found it almost impossible to judge precisely in advance just how large to cut the skin patch in the first place (Fig. 5).

Before the patch is completely closed, a 12 Fr. latex Foley catheter is left indwelling, or, in selected cases, a suprapubic catheter inserted.

5

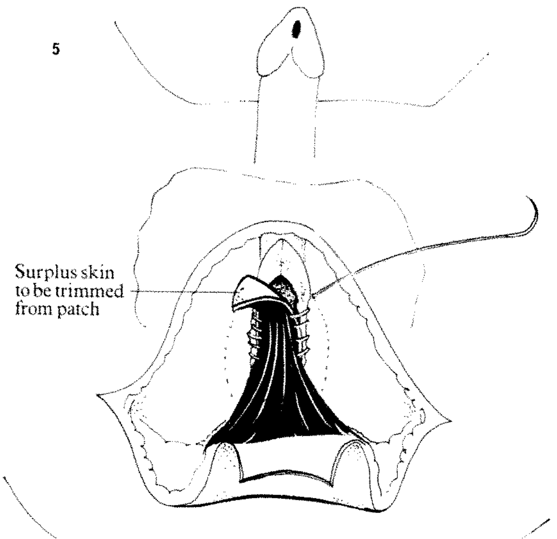

Fig. 5. Trimming away surplus skin.

6

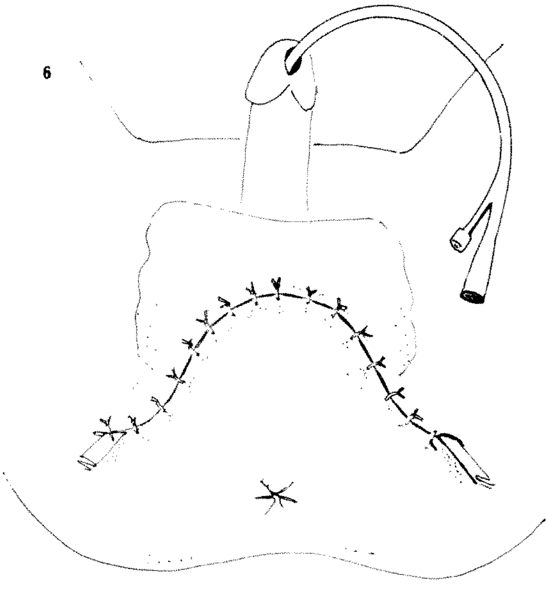

Fig. 6. The completed operation.

Table II

205 Urethroplasties: Methods Used

		%
Meatoplasty	22	10·7
Marion	1	0·5
Swinney 2 stage	8	3·9
Scrotal flap 2 stage	138	67·3
Tubed pull through	9	4·4
One-stage patch	27	13·2
	205	100·0

Table III

27 Island Patch Urethroplasties: Complications

Temporary fistula	1
Re-stenosis	1
Pulmonary embolism	1
Too large a patch	3
	6

The bulbospongiosus muscle is loosely approximated over the muscular pedicle of dartos supplying the patch, and the skin is closed with interrupted Nylon with two Penrose drains in either corner of the incision. As a precaution against postoperative haematoma formation a pad of "Reston" © sterile foam is applied over the perineum, and firmly secured with a T-bandage (Fig. 6).

Antibiotics are withheld unless there is any evidence of wound infection or urinary infection, except in the elderly patient, when we have been giving a suitable dose of crystalline penicillin in view of the theoretical danger of clostridial infection from a perineal incision.

The catheter is removed after 14 days, the sutures on the 10th postoperative day.

Results

27 one-stage patch urethroplasties have so far been performed: 20 involved the posterior urethra—one of these with a second patch to the anterior urethra in the standard Orandi method—6 were single anterior patches, and a 7th had two patches put in one behind the other.

The longest follow-up is 3 years. One patient (to date) has undergone a re-stenosis, the narrowing being at the anterior end of the patch, probably because the stricture was opened out insufficiently. He is awaiting a second operation. The others have not had any more instrumentation.

One patient developed a pulmonary embolism on the 8th postoperative day which responded to anticoagulants.

The main postoperative problem has arisen from failure to make the patch the right size for the urethra: in 3 patients the pouch has been too big and baggy: curiously enough, only one of these patients has complained of pooling of urine in the pouch, but our experience with two-stage urethroplasties suggests that as time goes by we may see hair-ball formation in the redundant pouch of urethra, and it may be necessary to trim away some of the surplus pouch at a second revision operation.

One symptom may be worth recording: some of these men have complained of a feeling of "wetness" in the scrotum: this is not incontinence, nor is it related to pooling of urine in the surplus urethra, but it seems to be related to preservation of the sensory nerve supply of the patch of scrotal skin which, lying in the lumen of the urethra, is kept moist.

Conclusions

Early experience with island flap modifications of well-tried methods of urethroplasty suggests that this is an excellent and reliable technique which can be recommended for straightforward strictures which are not unduly complicated by infection, false passages or fistulae. As with any method of urethroplasty, it is necessary to follow these patients for a long period of time before one can state with any certainty that re-stenosis will not occur: the natural history of urethral stricture is measured in decades, not in months.

Summary

27 one-stage island patch urethroplasties have been performed with the longest follow-up of 3 years.

The method seems to have most of the advantages of standard 2-stage scrotal flap urethroplasty, and is suited to all but the most difficult and complicated strictures at any site in the urethra.

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Immunological Effects of Orchidectomy

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The exact place of endocrine therapy in treatment of prostatic cancer is a matter for debate (Jewett, 1972) but there is little doubt that in some cases it can have profound beneficial effects on the disease (Huggins, Stevens and Hodges, 1941). The use of hormones for treating prostatic cancer was based on the observation that growth and proper functioning of normal prostatic tissues require a constant supply of testicular androgens; interference with them, either by castration or administration of oestrogens, being associated with prostatic atrophy. Because of the frequent histological and biochemical similarity of malignant and benign prostatic tissues it was argued that prostatic cancer should respond to endocrine therapy in the same way.

The initial effects of hormonal administration are to alter the whole hormonal environment but the more fundamental mechanisms which affect tumour growth are not clear. Changes in tumour growth could result from a direct effect on hormone-dependent cells for there is no doubt that alterations in circulating sex hormones affect vital cell functions directly (Talalay and Williams-Ashman 1960). Alternatively they might affect immunological reactivity for there is considerable evidence that an intimate relationship exists between the endocrine and immune systems (Kappas and Palmer, 1963; Ciba Foundation Study Group, 1970) and more specifically sex hormones have profound effects on immunological responses (Pierpaoli and Sorkin, 1968; Castro and Hamilton, 1972). Females are immunologically more competent than males and both in laboratory animals and humans incidence of tumours is lower in females. Whether the lower degree of immunity in males is genetic or hormonal in origin is not clear and therefore immunological effects of orchidectomy were studied.

Objectives

The objectives of this study were to see if orchidectomy affects immunological reactivity and to investigate any differential effects on separate arms of the immune response. Because of the association of immune status with tumour incidence, effects of orchidectomy on tumour induction and transplantation were studied.

Materials

Mice were from the breeding units of the National Institute for Medical Research and Clinical Research Centre, Harrow. Strains used in these experiments were Balb C, CBA and A strain.

The tumour used was a methylcholanthrene induced sarcoma (Meth A) obtained from, and described by Old, Boyse, Clark and Carswell (1962). We have confirmed that the tumour is antigenic, exhibiting a good dose response curve; on electron microscopy it does not contain viral particles and it is syngeneic for Balb C mice. Sheep anti-mouse thymocytes serum (a.l.s.) was used and 0·25 mg given subcutaneously for 3 days immediately before tumour inoculation.

Methods

All surgical operations were performed using intraperitoneal pentobarbitone sodium anaesthesia (Nembutal, Abbott diluted 1 : 10 with saline given at a dose of 0·1 ml/1 g body weight). Techniques of orchidectomy and

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thymectomy have been described previously (Castro, 1974*a*) and in control mice sham orchidectomy consisted of delivering testes to the wound surface, returning them to the abdomen and closure of the wound. Orchidectomy was performed at 4 weeks of age and immunological measurements made 6 weeks later.

Thymuses were weighed on a torsion balance immediately after removal. Androgen replacement consisted of 0·05 mg testosterone propionate in 0·1 ml corn oil given subcutaneously 3 times weekly.

Tail-skin allografts were transplanted to the dorsolateral thoracic wall by modifications of the methods of Billingham and Medawar (1951). Oxazolone is a skin-sensitising agent. The *in-vivo* response to it was measured by methods described by Davies *et al.* (1969) and a comparison of control and orchidectomised mice made by calculation of an index.[1]

After sensitisation, the response to S.III fraction of pneumococcal polysaccharide was measured by an agglutination technique. The direct response to sheep erythrocytes was measured at intervals after antigen by determining the number of plaque forming cells using modifications of the methods described by Cunningham (1965). Clearance of carbon particles, which is a measure of macrophage activity, was measured by the methods of Biozzi, Benacerraf and Halpern (1953).

Chemical tumours were induced by subcutaneous injection of 0·1 ml of 5 mg/ml 20-methylcholanthrene in olive oil and tumour volume was calculated by the method of Phillips and Gazet (1968).

Results

Thymus weights of 8 orchidectomised mice were significantly greater than controls 3 weeks after orchidectomy and androgen replacement prevented this (Table I).

Table I

Thymus Weight (mg)

Controls	Orchidectomised and Testosterone	Orchidectomised
45·2	35·4	53·4
36·6	34·0	84·0
37·8	46·0	58·0
39·0	44·2	73·0
41·8	41·6	82·2
29·4	32·0	62·8
26·4	31·0	71·0
29·2	38·0	52·4
Mean 35·6	37·7	67·1
S.D. 6·6	5·6	12·3

The effect of testosterone replacement on the thymus weight of orchidectomised mice. 0·05 mg of testosterone propionate in 0·1 m corn oil was given subcutaneously 3 times weekly. Thymus were weighed 3 weeks after orchidectomy.

15 Balb C mice were orchidectomised when 4 weeks old and skin grafted 6 weeks later with C3H skin. These grafts were rejected significantly faster ($P < 0{\cdot}05$) when compared with age-matched controls (Fig. 1).

4 days after skin painting with oxazolone the weight of draining lymph nodes was significantly greater in orchidectomised mice than controls and this difference was maintained when allowance was made for the differences of body and lymph node weight normally found in orchidectomised and control mice (Table II).

Pooled sera from 15 control and orchidectomised mice were used to determine antibody titres to S.III pneumococcal polysaccharide at intervals after antigen. There was no significant difference between the 2 groups (Fig. 2).

3 days after sheep erythrocytes there was no significant difference in the response of control and orchidectomised mice but by the fourth and fifth days after antigen it was significantly greater in orchidectomised animals (Table III).

[1] The index is: $\frac{\text{mg draining lymph node/g painted body}}{\text{mg draining lymph node/g unpainted body}} \times 100.$

Clearance of carbon particles was measured in 7 orchidectomised and 6 control mice. 10 minutes after carbon injection serum levels were significantly lower in the orchidectomised mice, indicating greater clearance (Table IV).

40 control and orchidectomised mice were injected with methylcholanthrene. 4 animals from each group died without tumour, in the remainder orchidectomy prolonged the interval between carcinogen and tumour (Table V).

Orchidectomy conferred slight, but significant, protection against ascitic Meth A tumour cells but a.l.s. counteracted this effect (Table VI).

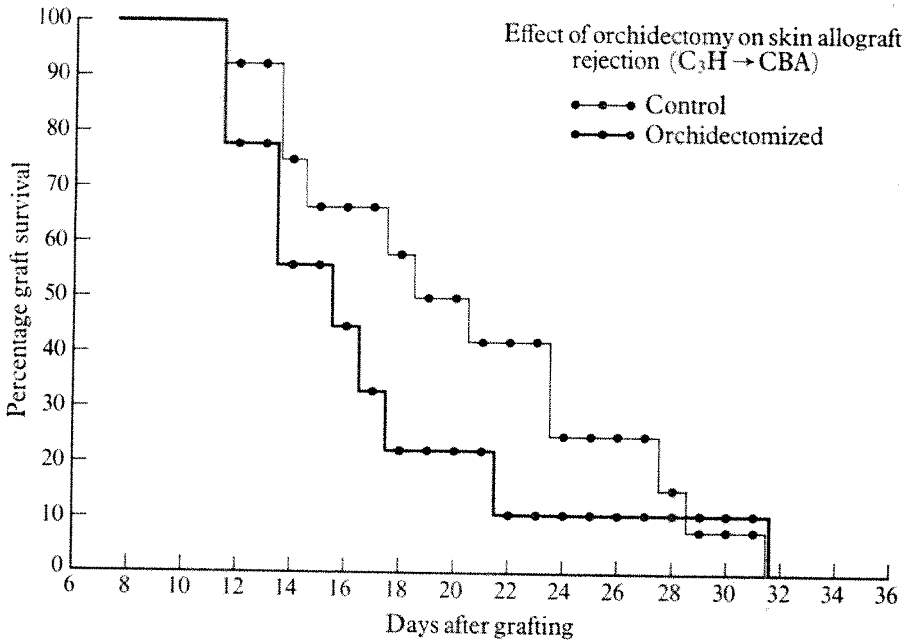

Fig. 1. The effect of orchidectomy on skin allograft survival (when graft donor and recipient do not differ at the major histocompatibility locus).

Table II

The Response of draining Lymph Node Weight in Control and Orchidectomised Mice 4 Days after painting with Oxazolone (mean values ± 1 S.D.)

Treatment	Body Weight (g)	Left Brachial and Axillary Nodes (mg)	Lymph Node wt/body wt.	Index*
Control mice	19·48 ± 2·57	5·42 ± 1·32	0·29 ± 0·08	232·18 ± 27·23
Controls + oxazolone	15·38 ± 3·03	12·53 ± 2·92	0·67 ± 0·08	
Orchidectomised mice	18·06 ± 1·22	5·98 ± 0·67	0·35 ± 0·05	333·33 ± 21·4
Orchidectomised + oxazolone	20·35 ± 1·85	23·10 ± 2·99	1·13 ± 0·77	

$$* \text{ Index} = \frac{\text{Weight of draining nodes (mg)/body weight (g) painted}}{\text{Weight of draining nodes (mg)/body weight (g) unpainted}} \times 100$$

t test: Index in control *vs.* index in orchidectomised $t = 7{\cdot}157$

Control node weight *vs.* orchidectomised node weight $t = 6{\cdot}195$

Control corrected node weight *vs.* orchidectomised corrected node weight $t = 10{\cdot}614$

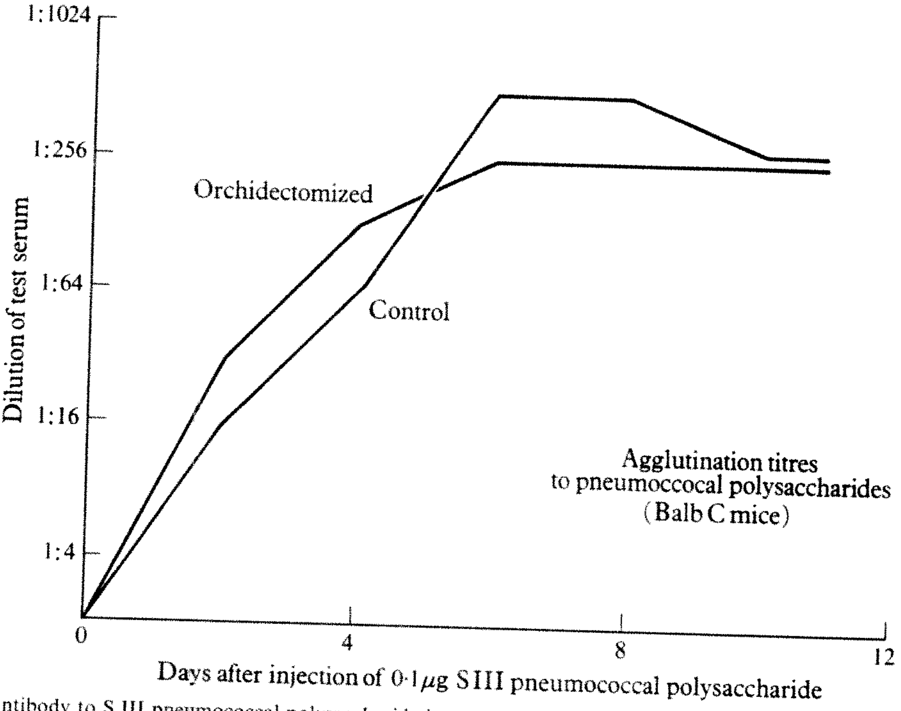

Fig. 2. Antibody to S.III pneumococcal polysaccharide in control and orchidectomised mice at intervals after S.III.

Table III

Plaque Forming Cells/Spleen in Control and Orchidectomised Mice

Days after Antigen	Mean P.F.C./spleen ± S.D.	
	Control	Orchidectomised
3	6503 ± 882	7640 ± 1042
4	32715 ± 3686	44050 ± 3803
5	29020 ± 3534	37220 ± 3611

Discussion

Several lines of evidence suggest that there are at least two distinct types of immunocompetent lymphocytes (Raff, 1969; Raff, Nase and Mitchison, 1971). One group of lymphocytes, T-cells, require the thymus for development and they are responsible for cell-mediated immunity. The other, referred to as B-cells, develop independently of the thymus and they mediate humoral antibody responses.

Results described here suggest that orchidectomy has its main effects upon thymus-derived cells. Orchidectomy caused enlargement of the thymus which could be abrogated by androgen and similar effects have been observed in other lymphoid organs (Castro, 1974*b*). Other experiments (Castro, 1974*c*) suggest that this effect of orchidectomy results directly from androgen withdrawal rather than changes of trophic hormones.

Table IV

To show Levels of Carbon in Control and Orchidectomised Mice at the Time of Injection of Carbon Particles and 10 Minutes later (means for 6 mice)

	Controls			Orchidectomised		
	0 min	10 min	Difference	0 min	10 min	Difference
Mean	0·819	0·720	0·099	0·850	0·643	0·221
S.D.	0·048	0·035	0·067	0·085	0·049	0·083

Control differences *vs.* orchidetomised difference. $t = 49{\cdot}78$.

Table V

To show the Percentage of Mice surviving after Subcutaneous Injection of Methylcholanthrene (MC)

	Days after MC				
	50	100	150	200	250
Controls	100	89	36	17	10
Orchidectomised	100	90	54	45	35

Table VI

To show the Effects of ALS on the Tumour Protective Effect of Orchidectomy

	Days after Meth A Tumour Cells i.p.				
	10	15	20	25	30
Control	100	15	5	0	0
Orchidectomised	100	40	15	15	15
Control + ALS	78	14	0	0	0
Orchidectomised + ALS	100	0	0	0	0

Sheep antimouse ALS 0·25 ml was given for 3 days before challenge with $3{\cdot}5 \times 10^3$ Meth A tumour cells. Orchidectomy was 4 weeks before ALS.

Concomitant with these structural changes there was alteration of immunological reactivity, for orchidectomy was associated with an increased response to some antigens. Some antigens depend on T-cells for their expression, others are thymus independent whilst some depend upon interaction between both classes of lymphocytes.

Rejection of skin allografts and the early response to oxazolone are functions of cell-mediated immunity (Miller, 1965; Davies *et al.*, 1969). Orchidectomy caused accelerated rejection of skin allografts and an increased early response to oxazolone; findings suggestive of increased cell-mediated immunity after orchidectomy. The observation (Castro, 1974*d*) that accelerated graft rejection can be prevented by thymectomy or a.l.s. (which inhibit cell-mediated immunity) is further evidence on this point.

Pneumococcal polysaccharide is probably the most thymus-independent antigen (Davies *et al.*, 1970). Response to it was not increased after orchidectomy, which suggests that B-cells function is unaffected.

The response to sheep erythrocytes requires both B-cells for antibody production and T-cells in a helper role (Mitchell and Miller, 1968). Increased antibody in orchidectomised mice could reflect changes in either population, but recent work (Campbell 1972) suggests that the reaction is limited by T-cells so the increased response represents increased T-cell function.

There is considerable evidence that the immune system plays an important role in tumour destruction both in laboratory animals (Foley, 1953; Prehn and Main, 1957) and in man (Nadler and Moore, 1966; Penn and Starzl, 1972). There is, however, disagreement as to the relative roles of cell-mediated immunity (Alexander and Fairley, 1967), antibodies (Karush and Eisen, 1962) and macrophages (Castro, 1974*e*). Orchidectomy is associated with increased T-cell function, a slight increase of macrophage activity and no obvious effect on B-cell function. It also decreased death rate from chemically induced and transplanted tumours although the growth rate of established tumours was unaffected. The association of increased cell-mediated immunity with tumour protection may be fortuitous, but the observation that a.l.s. inhibited the tumour-protective effects of orchidectomy suggest that it is the mechanism whereby protection is afforded.

Tumours used in these experiments were not from tissues usually considered to be endocrine dependent and this was confirmed by the ability to grow them *in vitro* without hormonal supplements and by growing both tumours in recipients of either sex.

It is generally thought that endocrine treatments act directly on the cells of endocrine-dependent tumours. The findings described in this paper suggest that at least some of the anti-tumour activity may result from alterations of host immunity.

Summary

Orchidectomy caused a non-specific increase of immunological reactivity in mice evidenced by accelerated rejection of skin allografts, increased response to oxazolone and sheep erythrocytes. These changes were associated with an increase of thymic size.

The response to pneumococcal polysaccharide, which depends upon B-cells, was not increased.

Orchidectomised mice showed protection against induced methylcholanthrene sarcomas and transplantable tumours; tumours which are not obviously hormone dependent.

Table I is reproduced from the *Journal of Endocrinology*.

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The Diagnostic and Prognostic Significance of Delayed Hypersensitivity Skin Testing in Patients with Urological Cancer

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There is considerable evidence for the importance of immunological mechanisms in the control of cancer both in animals (Foley, 1953; Delorme and Alexander, 1964; Rapp, 1968) and man (Hellstrom *et al.*, 1968; Sophocles and Nadler, 1971). Patients with impaired immunological competence have an increased incidence of tumours (Dent, Petersen and Good, 1968; Penn and Starzl, 1972) and patients with malignant tumours may fail to respond to cutaneous antigenic stimulation (Hughes and MacKay, 1965; Solowey and Rapaport, 1965).

This study was undertaken to investigate cellular immunity in patients with cancer of the bladder or prostate by assessing their cutaneous delayed hypersensitivity responses to four antigens, di-nitrochlorbenzene (DNCB), Candida extract, streptokinase/streptodornase (SKSD) and purified protein derivitative (PPD). It is unlikely that patients would have made previous contact with DNCB and the response to sensitisation with it, is a test of the ability to react to a new antigen. The other three antigens are recall antigens and a response to them depends upon previous infection with sensitisation, a negative response may therefore reflect either diminished immunological reactivity or no previous contact with the appropriate antigen.

Responses to these antigens in patients with cancers of the bladder and prostate have been compared with controls. The findings have been correlated with the stage of the tumour, the effects of treatment and the survival of the patient.

Materials and Methods

Patients

All patients attending with symptoms or signs suggestive of bladder or prostatic cancer were studied. After investigation, 15 patients (12 male and 3 female) with ages ranging from 47 to 71 years (mean 62 years) were found not to have a malignant lesion and these were controls.

21 patients with histologically proven prostatic cancer aged 56 to 84 (mean 71 years) and 59 patients (47 male, 12 female) with ages ranging from 40 to 86 years (mean 66 years) who had histologically proven bladder cancer were studied.

Certain factors impair the immune response and for this reason patients with blood ureas above 100 mg% and patients who had received radiotherapy or cytotoxic chemotherapy within the previous 3 months were excluded from the study. Tests were not performed within 3 weeks of general anaesthesia.

DCNB Sensitisation and Testing

Sensitisation of patients to DNCB was attempted by 0·1 ml of a 5% solution of DNCB (BDH Chemicals) in acetone, applied to the absorbent part of a 3·8 cm^2 airstrip adhesive dressing (Elastoplast), and allowed to dry.

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

The treated plaster was then placed on the volar aspect of the patient's right forearm. To test for previous chance sensitisation 0·1 ml of 0·1% DNCB was applied in the same way to a different part of the forearm. Both plasters were removed 72 hours later.

The response to sensitisation was tested 14 to 21 days later by applying 0·1 ml of 0·1% DNCB as previously described and observing the test 48 hours later. An area of erythema and induration involving more than half the test site was recorded as a positive response. If there was a negative response the test dose was re-applied and read again after 48 hours.

Recall Antigens

Candida extract (Hollister Stier Laboratories), SKSD (Lederle Laboratories) and PPD (Evans Laboratories) were given as intradermal injections on the volar aspect of the forearm. A positive reaction was recorded if an area of erythema and induration more than 5 mm in diameter was present 48 hours after injection.

Results

No systemic reactions were observed to any of the antigens. 3 patients developed blistering at the site of the sensitising dose of DNCB, but this healed rapidly with no residual scarring after treatment with topical steroids. In some patients pigmentation at the site of sensitisation with DNCB remained for up to 6 weeks.

Reactivity to DCNB

None of the patients, either control or with tumour, showed chance sensitisation to DNCB (Table I).

Table I

Ca. Prostate Response to DNCB

Control		Overall		Stage O Incidental		Stage II-III		Stage IV	
No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested
15	15	21	21	5	5	9	9	7	7

Incidence of delayed cutaneous hypersensitivity to DNCB in control group and those with carcinoma of the prostate.

All 15 control patients were sensitised to DNCB and reacted to the test dose. Similarly, all 21 patients with prostatic cancer reacted to the test dose (Table I) despite differences in the stage of the disease and the treatment given. 13 of 16 patients with advanced prostatic cancer were already being treated by oestrogens, orchidectomy or a combination of the two at the time of treatment.

43 of 54 patients (80%) with carcinoma of bladder showed a positive response to testing with DNCB (Table II). The incidence of a positive response was related to the stage of the tumour and prognosis. All of the patients who had been free from tumour for more than 1 year responded but a highly significant number of patients with advanced disease (Stages 3 and 4) failed to respond to DNCB (Table III). Failure to respond to repeated test doses of DNCB was associated with a bad prognosis, for 7 of 8 such patients died within 3 months of the first test. 2 patients who did not respond initially converted to positive responses after total surgical removal of their tumours. 1 patient who had an initial positive response now shows no response and this is associated with recurrence of tumour.

Table II

Ca. Bladder Response to DNCB

Control		Overall		Tumour Free 1 Year		Tumour Free 5 Years	
No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested
15	15	43	54	14	14	13	13

Incidence of delayed cutaneous hypersensitivity to DNCB in the control group and those with carcinoma of the bladder who had been free of tumour for more than 1 year.

Table III

Ca. Bladder Response to DNCB

Control		Stage I		Stage II		Stage III		Stage IV	
No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested
15	15	26	28	12	12	2	5	1	6

Incidence of delayed cutaneous hypersensitivity to DNCB comparing one control group with 4 stages of bladder carcinoma.

Controls *v*. Stage III—P by Fishers Extract Test = 0·009.
Controls *v*. Stage IV—P by Fishers Extract Test = 0·0003.

Reactivity to Recall Antigens

The responses of patients with cancers of the prostate and bladder to individual recall antigens and to all 3 recall antigens have been observed. The only significant finding was the inability of patients with advanced bladder tumours to mount a response to PPD (Table IV). There was no correlation between the response to candida or SKSD with the stage of the disease or response to treatment. Neither was there a correlation when the collective responses to antigens was observed.

Discussion

This study showed that delayed hypersensitivity skin testing could be simply performed with minimal morbidity in patients with urogenital cancer.

The results show a clear and previously unreported difference in response to DNCB between those patients with cancer of the prostate and those with cancer of the bladder. The finding that all patients with prostatic cancer reacted to DNCB, irrespective of the extent of the tumour or the therapy, is interesting. 13 of the 16 patients studied had been treated by orchidectomy or oestrogens and both of these treatments may affect immunological reactivity. Orchidectomy increases the immunological response of mice to a variety of antigens particularly those that depend upon cell mediated immunity for their expression (Castro, 1974). Oestrogen administration causes atrophy of lymphoid tissues, but oestrogenic enhancement of natural or induced circulating antibody levels have been observed in many (von Haam and Rosenfeld, 1942) but not all reports

Table IV

Ca. Bladder Response to Skin Test Antigens

	Controls		Stage I		Stage II-III		Stage IV	
Antigen	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested
PPD	11	11	7	15	6	9	2	6
SKSD	8	11	8	17	3	9	5	6
Candida	7	11	5	17	5	9	2	6

Incidence of delayed cutaneous hypersensitivity to the recall antigens in patients with carcinoma of the bladder compared with the control group.

PPD controls *v.* Stage I —P by Fishers Extract Test = 0·007.
PPD controls *v.* Stage II/III—P by Fishers Extract Test = 0·07.
PPD controls *v.* Stage IV —P by Fishers Extract Test = 0·006.

(Warr and Slijivic, 1972) and oestrogens have stimulatory effects on macrophage activity. These effects of endocrine manipulations on the immune response could explain most of our results, but 3 patients with advanced prostatic cancer had not received endocrine treatment yet reacted to DNCB. Until the mechanisms of non-specific immune depression (anergy) in patients with advanced tumours are more clearly understood it is not possible to explain these findings.

In patients with bladder cancer there was good correlation between reactivity to DNCB and the stage of the tumour and prognosis. However, a number of patients who had advanced bladder cancer but who are not included in this study because they were uraemic or receiving cytotoxic chemotherapy died from their disease whilst still reacting to DNCB. The use of graded test doses of DNCB so that a dose response curve is obtained may be a more accurate method for assessment of such patients.

Whilst there is little doubt that host response is important in tumour growth it is not clear whether failure to respond to non-specific antigens is the cause of tumour dissemination or whether it is a consequence of it. Factors within the host which influence immune status are probably legion (Kongshavn and Lapp, 1972) but the immunosuppressive effects of inadequate nutrition (Jose and Good, 1972) and cortisone (Medawar and Sparrow, 1956) are well known and they may contribute to non-specific immune depression in patients with advanced malignancy.

The results of skin testing with candida antigen, SKSD and PPD were of little value in the assessment of patients with urogenital cancer. Only the response to PPD showed some correlation with the stage of the bladder cancer. However, response to these recall antigens depends upon previous natural sensitisation; a negative reaction may result from either anergy associated with malignancy or the absence of previous sensitisation. Changes in the response to repeated tests with recall antigens may be more valuable in assessment of patients with malignancy but such testing may be associated with severe allergic reactions.

Summary

The responses to several skin test antigens of patients with bladder or prostatic cancer has been compared with responses of normal controls.

All of the controls and all of the patients with prostatic cancer (irrespective of the stage of the tumour or the method of treatment) showed responses to dinitrochlorbenzene. 80% of all patients with bladder cancer responded to DNCB, but a highly significant number of patients with advanced disease showed no response. This test appears especially useful in predicting the prognosis in patients with bladder tumours and its routine use is recommended.

Response to candida extract, streptokinase/streptodornase (SKSD) and purified protein derivative (PPD) were also studied. No conclusion could be drawn as to their value as a prognostic index.

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British Journal of Urology (1975), **47**, 103

A Look at the Three-way Catheter[1]

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The 3-way catheter has become popular with the urologist as a means of draining and irrigating the bladder after transurethral prostatectomy. However, many of the available catheters of this type have a very small lumen to the input tube which is used for irrigation because of the mistaken belief that an input tube of greater diameter would mean a smaller output tube for a given size of catheter and consequently poorer drainage.

When the dynamics of these catheters are studied it becomes clear that efficient drainage depends more on the flow rate than on the actual size of the lumen of the output tube. This is because a fast flow will prevent the blood clots forming and accumulating in the bladder. This can be achieved only with a larger input tube, and experimental work shows that to double the flow rate into the bladder a small increase only is needed in the size of the tube, and the corresponding reduction in the outflow tube is of no serious consequence.

Many of the available 3-way catheters were compared and their ability to clear an experimental "bladder" of a coloured dye. With the normal height of drip stand and length of catheter the suggested internal diameter of the input tube is 2 mm as this will achieve twice the flow rate of the commercially available catheters which were studied.

The author is interested in discussing this problem with others similarly interested or with any catheter manufacturers who would be prepared to develop improved 3-way catheters.

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[1] A Summary of an Essay which won the Simpla Urological Prize on "Disposable Equipment in the Urological Field—Desirable Standards and Thoughts on Future Development". The prize was awarded by Simpla Plastics Ltd.

Book Reviews

The Kidney. By H. E. DE WARDENER. 4th Edition. Pp. viii + 432 with 113 illustrations. Edinburgh: Churchill-Livingstone. 1973. £5.

The fact that this book has run into 4 editions in the space of 15 years attests not only to its popularity and the energy and dedication of its author but also to the remarkable progress which has been made in the field of renal medicine during the past two decades. In general Professor de Wardener has coped very well with the difficult task of introducing new and often complex and controversial topics into a monograph which is designed to provide undergraduate and junior postgraduate students with an understanding of renal disease. This is well exemplified by the new section on immunological disorders in which he makes a very gallant effort to clarify the somewhat confusing picture of glomerulonephritis which has emerged from the increasing use of immuno-fluorescent staining techniques and electron microscopy. In this and other sections of the text which deal with normal and abnormal microscopic anatomy the simple outlined diagrams are immensely helpful. These have always been an outstanding feature of the book and with their aid most readers, even those that tend to shy at the sight of a photo-micrograph, should be able to gain some insight into the ultrastructure of the kidney in health and disease without too much mental trauma. The section on renal infections also merits special praise for its somewhat radical but remarkably rational approach, though some may question the author's belief that a surreptitious ingestion of phenacetin is one of the main causes of a gradual deterioration in renal function in chronic childhood pyelonephritis. Of course, it is always possible to find something to criticise in a monograph which sets out to cover a wide and rapidly developing field and doubtless most teachers of nephrology will find that they disagree with some of Professor de Wardener's views. Nevertheless, this book must have far more educational value than any other undergraduate textbook on nephrology and, as such, it can be confidently recommended to the student who is really interested in the kidney and not simply anxious to brush up his nephrology for examination purposes. It remains to be said that the book is commendably free of typographic errors, though the rather complex little section on defects in the tubular handling of sodium is made even more confusing by the statement that patients with Bartters syndrome present with the symptoms of hyperkalaemia.

A. R. H.

Acute Renal Failure. Edited by C. T. FLYNN. Pp. 147, 19 illustrations. Medical and Technical Publishing Co. Ltd. 1974. £4·50.

This chatty little book consists of the edited proceedings of a symposium held on the subject of acute renal failure organised by the RAF medical services. A series of talks were given by invited speakers. These, and the discussions which followed, have been faithfully reproduced. The book starts well with good sections on the pathogenesis of acute renal failure and the value of radiology in acute renal failure, but thereafter it tends to tail off into a series of clinical impressions and anecdotes. Here and there some good points are made and occasional gems of clinical wisdom appear in the discussion. The book can be read effortlessly and quickly and will be entertaining to nephrologists who were unable to get to the meeting; it is also slightly instructive to non-nephrologists who would like to know what nephrologists think about these matters. It provides a painless way of acquiring some useful practical information.

P. R. U.

Postgraduate Nephrology. By R. GABRIEL. Pp. 216, 21 illustrations. Butterworth and Co. Ltd., 1974. £2·25.

Attempts to write short concise textbooks for cramming purposes on complicated and controversial topics are bound to lead to over-simplication and dogmatic statements with which experts will disagree. This short paperback, written primarily for the MRCP candidate with insufficient time or inclination to read more authoritative texts, is no exception. Nevertheless, Dr Gabriel has managed to gather a fairly large amount of mainly accurate and useful information into a readable book which will no doubt prove valuable to those who like acquiring knowledge in this way. It will serve as a convenient means of quick revision. Many will disagree with such statements as "there are no specific electron microscope abnormalities" in minimal change glomerulonephritis—at least if the statement is not qualified or elaborated in any way. Typographical errors are disconcertingly frequent and one hopes that this work, which does fulfil a useful function, will be considerably polished and improved for the second edition.

P. R. U.

Benign Enlargement of the Prostate. By K. E. D. SHUTTLEWORTH, R. W. LLOYD-DAVIES and R. GREENE. 1st Edition. 120 pages, 89 illustrations. London: Heineman Medical Books. 1973. £4·00.

Is your operation really necessary? So many prostates are removed annually that occasionally one suspects that the indication for surgery is "because it is there"—and the patient is over 60. In 115 pages this book gives a remarkably comprehensive account of benign enlargement of the prostate. The discerning reader should be able to avoid too many unnecessary operations. The non-specialist will realise, too, that the bladder is perhaps a rather more subtle organ than he realised. The first 5 chapters on the pathology, diagnosis and indications for treatment of benign hyperplasia could be read with benefit by physicians and budding surgeons alike. Chapters on the surgery and postoperative management of the prostate are nicely balanced and again could be studied by our non-surgical colleagues who are so often called in to advise during the management of these patients. There are, of course, many points of detail with which one could disagree: after all, no two surgeons take out a prostate in quite the same way. But these are minutiae; the novice who followed the advice in this book would be safe and do well for his patients.

This is an excellent introduction to prostatic surgery which can be recommended to any trainee surgeon and could be read with profit by physicians and general practitioners as well. There is, however, one potential drawback which is built in to a book such as this which discusses only a single disease. Prostatic diseases, benign, malignant or inflammatory, are so inextricably entangled, and they in turn are so bound up with the problems of bladder function, that the beginner may get an unbalanced picture of the problem. A short chapter sufficient to indicate the extent of the diagnostic problem would be of value.

D. M. E.

Abdominal Echography. By E. BARNETT and P. MORLEY. 1st Edition. (Series: Radiology in Clinical Diagnosis. Gen. Ed. David H. Trapnell.) Pp. x+138 with 143 illustrations. London: Butterworths. 1974. £4·50.

This surely is the ideal format for a modern medical textbook. This splendid little book contains all one could possibly need to know of clinical ultrasound as applied to the abdomen written by the established experts. So often books are out of date before they are published, but here the references indicate that the book has been rushed from the authors' pens to the bookshops. There are no signs of hurry, however. It is a beautifully produced book packed throughout with excellent examples of B Scans of every abdominal condition in which ultrasound is useful, from diseases of the liver to prostate.

The authors rightly do not claim echography to be a diagnostic panacea but instead stress both its usefulness and its limitations. Its main advantages are that it is painless, non-invasive and readily repeatable.

Examination of the kidney and bladder is discussed in the urological section. In practice the important contribution of ultrasound is in the differential diagnosis between a renal cyst and a carcinoma as time and again with its use the patient can be spared an arteriogram. A cyst must of course be punctured but ultrasound probes are now available which incorporate a needle to make this safe and simple. Its application to the bladder and prostate is interesting but unlikely to offer much extra clinical information.

With the high quality and quantity of the illustrations in this book it is excusably a little expensive for its 138 pages, but is a must for any department using or planning to use these techniques.

R. H. W.

Books Received

Genetics and the Urologist. By J. K. ORMOND and others. Springfield, Ill., Thomas, 1972. $10.75.

Notices

THE ROYAL SOCIETY OF MEDICINE

Section of Urology

PROGRAMME FOR 1974/5 SESSION

3rd APRIL Joint Meeting with Section of Pathology (Bacteriology) and the Medical Society for the Study of Venereal Diseases.

6.00 p.m. Non-specific Urethritis—Dr Eric Dunlop, London Hospital.
Virology of Non-specific Urethritis—Dr Darougar, Inst. of Ophthalmology.
Bacteriology

7.00 p.m. Buffet Supper.

8.00 p.m. *Chronic Prostatitis*

(*a*) Dr J. K. Oates, Westminster Hospital.
(*b*) Dr David Reeves, Bristol.
(*c*) Surgeon Captain Norman Blacklock, Royal Naval Hospital, Haslar.

26th APRIL Visit of the Section to the Department of Urology at Leeds.

22nd MAY Visit of the Section to the London Hospital.
Annual General Meeting.
Annual Dinner at the Royal Society of Medicine.

BRITISH ASSOCIATION OF UROLOGICAL SURGEONS

At The Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London, WC2A 3PN

President: Mr R. A. Mogg, V.R.D., M.Ch., F.R.C.S.

ANNUAL MEETING 1975—*Preliminary Announcement*

The Annual Meeting will be held at the University Hospital of Wales, Cardiff, on Wednesday, Thursday and Friday, 25th 26th and 27th June. A full programme will be circulated later, but the provisional arrangements are as follows:

WEDNESDAY, 25th JUNE

Morning	9.00 a.m. onwards	Registration.
	10.00 a.m.	Paediatric Urology.
Afternoon	2.00 p.m.	Scientific Session.
Evening	7.00-8.00 p.m.	Reception at the Welsh National Museum by invitation of the President and Council of the Association.

THURSDAY, 26th JUNE

Morning and Afternoon	Short Papers.
Evening	Annual Dinner at the Angel Hotel.

FRIDAY 27th JUNE

Morning		Short Papers.
Afternoon	2.00 p.m.	Annual General Meeting.
	2.30 p.m.	Report on the survey on urological needs carried out by the London School of Hygiene and Tropical Medicine. and Discussion on "Training Programme for Urologists".

SATURDAY, 28th JUNE

A visit to the new University Hospital has been arranged for the morning.

Ladies' Programme

A visit to Symond's Yat, near Ross-On-Wye, has been arranged for Thursday, 26th June. Further details will follow at a later date.

Hotel Accommodation

Accommodation has been reserved at the hotels listed below. **Your reservation should be made direct with the hotel of your choice, indicating that your booking is in connection with the B.A.U.S. Annual Meeting.**

The Angel Hotel, Cardiff, CF1 2QZ. Tel. No.: 0222 32633. 74 rooms (double, twin and single rooms with bath; twin rooms without bath) have been reserved **until 1st May 1975.**

The Centre Hotel, Westgate Street, Cardiff. Tel. No.: 0222 388681. 60 double and single rooms have been reserved **until 1st May 1975.**

The Park Hotel, Park Place, Cardiff, CF1 3UD. Tel. No.: 0222 23471. 53 double and single rooms have been reserved **until 1st May 1975.**

The Post House Hotel, Church Road, Pentwyn, Cardiff. Tel. No.: 0222 750121. 12 double and single rooms have been reserved **until 1st May 1975.** This hotel is situated on the Motorway, 1½ miles from the University Hospital of Wales: The Motorway also passes the Hospital.

Transport

Buses to and from the University Hospital will only be provided for those members staying at the Angel, the Centre and the Park Hotels.

Nominations for Council

The attention of members is drawn to the following Rule:

> "Candidates for the Full Member representatives on the Council shall be nominated by two Full Members at least six weeks before the Annual General Meeting, and shall give their written consent to stand. Candidates for the Associate Member representatives on the Council shall be nominated by two Associate Members at least six weeks before the Annual General Meeting, and shall give their written consent to stand."

Three Full Members and one Associate Member of Council will be retiring in 1975 and nominations for the vacancies must be sent to the Honorary Secretary **not later than 16th May 1975.**

J. P. WILLIAMS
Honorary Secretary

December 1974

THE BRITISH ASSOCIATION OF UROLOGICAL SURGEONS

TRAVELLING FELLOWSHIP 1975

The British Association of Urological Surgeons offers a Travelling Fellowship of £250 based on the best paper published in the *British Journal of Urology* in 1975 or papers presented at the 1975 Annual Meeting.

Authors of papers with multiple authorship should decide which of their number is to receive the Fellowship in the event of their contribution being selected.

Candidates for the prize must be Fellows of one of the Royal Colleges of Surgeons in the British Isles, Canada, Australasia or South Africa who are in the course of urological training or who have obtained consultant posts within ten years of the date of submission of the paper.

Three assessors will be appointed by the Council to make recommendations on the award of the Fellowship, which will be decided at the March B.A.U.S. Council meeting. The Council reserve the right not to make an award in any one year.

The award will be announced at the 1976 June meeting of the Association.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The list of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal, i.e.* in anatomical order beginning with papers on the kidney.

A general section is included at the end.

KIDNEY

Congenital Anomalies. Diagnosis and treatment of diseased horse-shoe kidney. (M. Kumar *et al.*) *Int. Surg.* 1974, **59**, 159.

Agenesis of the gallbladder, malrotation of the gut and horseshoe kidney. A new syndrome? *Amer. J. Surg.* 1974, **127**, 596.

Renal tract disease in imperforate anus. (M. P. Singh *et al.*) *J. Pediat. Surg.* 1974, **9**, 197.

Diagnosis and treatment of congenital small kidneys. (J. L. André *et al.*) *J. Urol. Nephrol.* 1974, **80**, 400.

Renal abnormalities in the Russell-Silver syndrome. (Z. Spirer *et al.*) *Pediatrics*, 1974, **54**, 120.

Hypervitaminosis A and congenital renal anomalies in a human infant. (I. B. Bernhardt and D. J. Dorsey.) *Obstet. Gynec.* 1974, **8**, 750.

The silent kidney in congenital abnormalities. (P. Hennebert.) *Acta Urol. Belg.* 1974, **42**, 78.

Radionuclide evaluation of crossed renal ectopia. (M. A. Razzak.) *Strahlentherapie*, 1974, **147**, 258.

Origin of the inferior mesenteric artery from the renal artery in fused crossed renal ectopia. (M. A. Madayag and M. A. Bosniak.) *Brit. J. Radiol.* 1974, **47**, 230.

Congenital anomalies of the left renal vein: angiographic consideration. (V. P. Chuang *et al.*) *Brit. J. Radiol.* 1974, **47**, 214.

Thoracic kidney. (L. Leite de Noronha *et al.*) *Amer. Rev. Resp. Dis.* 1974, **109**, 678.

Trauma. Post- traumatic pyelo-jejunal fistula with syndrome of urinary loss. (M. le Guillou *et al.*) *J. Urol. Nephrol.* 1974, **80**, 320.

Posttraumatischer Nierenarterienverschluss. (P. Brücke *et al.*) *Mschr. Unfallheilk.* 1974, **77**, 304.

Reversible Ektasie des Nierenhohlsystems traumatischer Ätiologie [Reversible ectasia of the renal pelvis of traumatic origin]. (F. Horváth *et al.*) *Fortschr. Röntgenstr.* 1974, **120**, 754.

Renal vascular damage after birth. *Brit. Med. J.* 1974, **3**, 296.

Bilateral avulsion of the renal pedicles by closed trauma. Report of one case. (J. Pillet *et al.*) *Chirurgie* 1974, **100**, 441.

Traumatic renal hemorrhage treatment by arterial embolization. (M. Kalish *et al.*) *J. Urol.* 1974, **112**, 138.

Traumatic right renal aneurysm. Conservative surgery. (J. Verges.) *J. Urol. Nephrol.* 1974, **80**, 313.

Traumatic diaphragmatic hernia of the left kidney. (M. Ribet *et al.*) *Chirurgie*, 1974, **100**, 237.

The radiology of renal trauma: a local survey. (M. R. Fuston.) *S. Afr. Med. J.* 1974, **48**, 981.

Nierenspontanrupturen als renale Komplikation der Cumarintherapie. Spontaneous rupture of the kidney after phenprocoumon therapy. (L. Weissbach *et al.*) *Deutsch. Med. Wschr.* 1974, **99**, 1135.

Traumatic injuries of the renal vasculature and parenchyma. (M. Koenigsberg *et al.*) *Seminars Nucl. Med.* 1974, **4**, 117.

The diagnosis and management of acute renal injuries. (D. R. Barnes.) *S. Afr. J. Surg.* 1974, **11**, 233.

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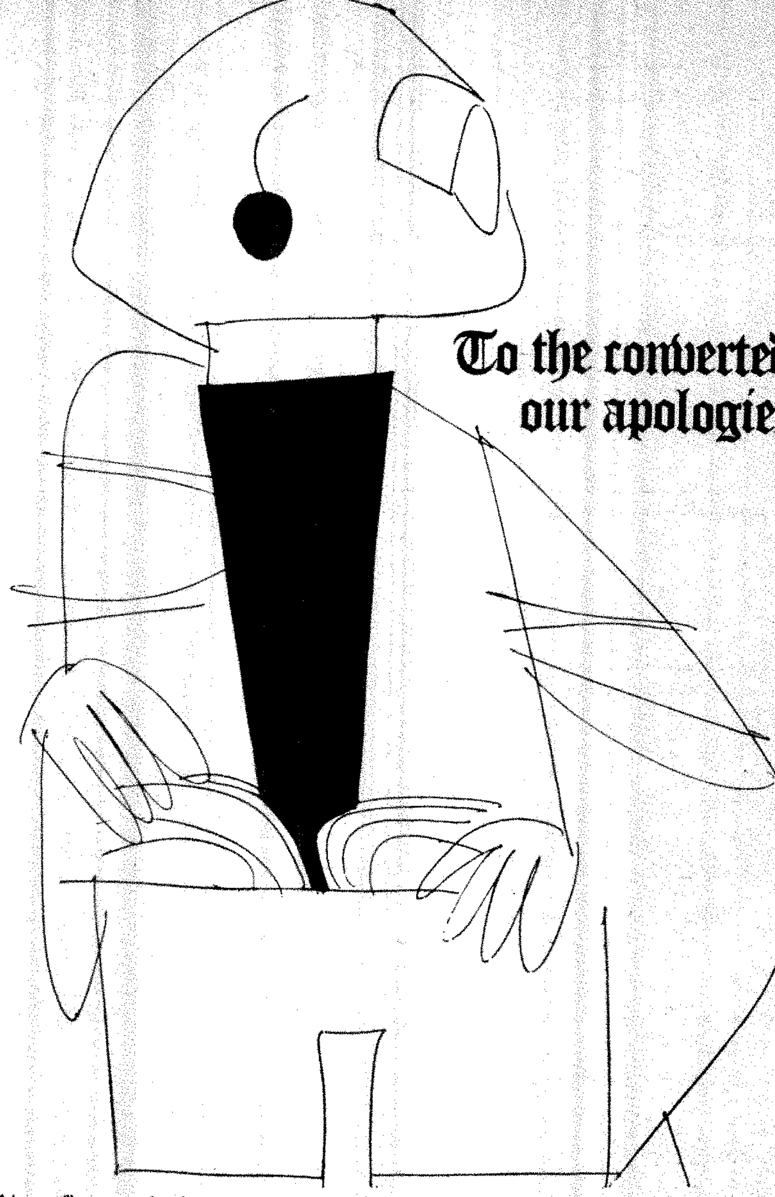

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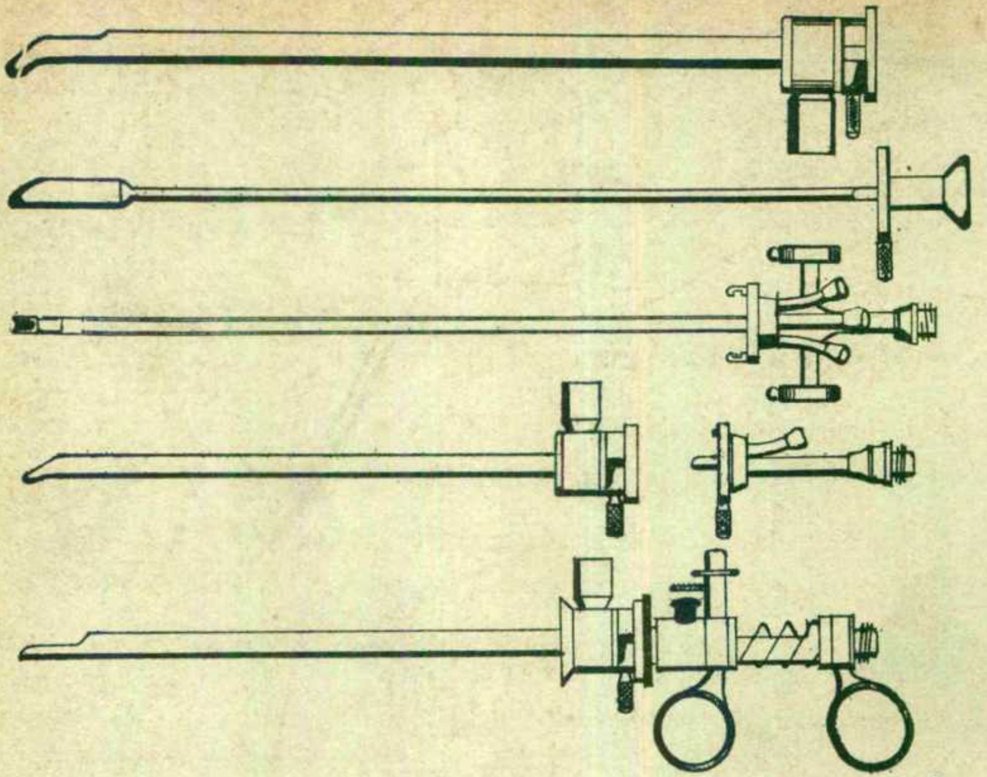

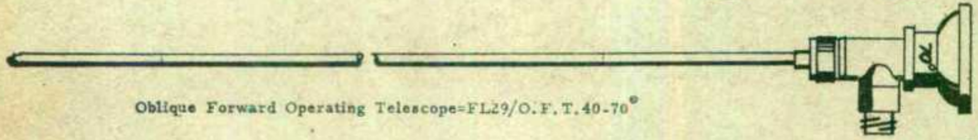

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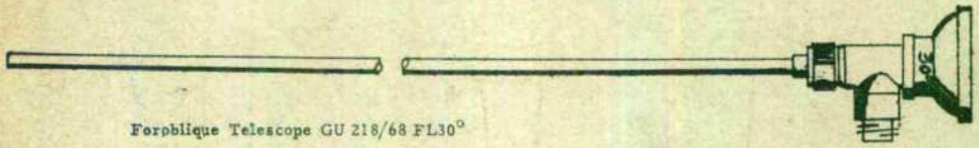

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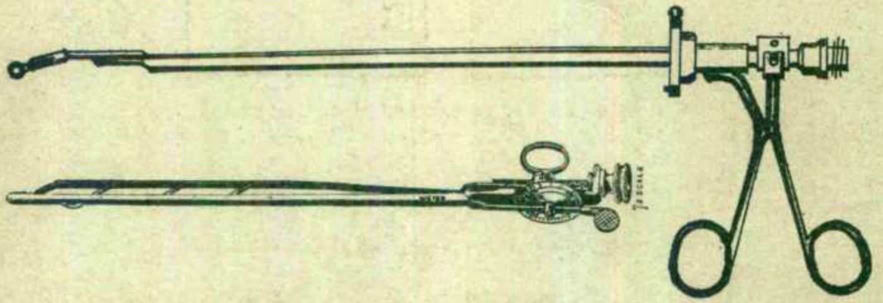

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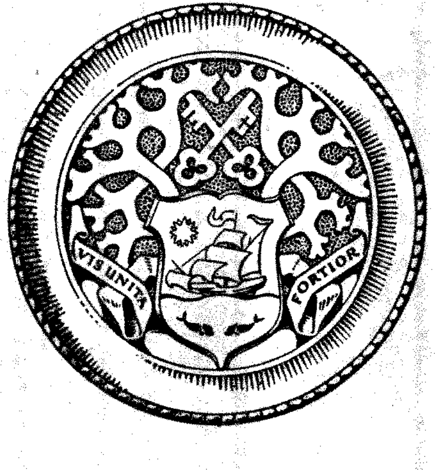

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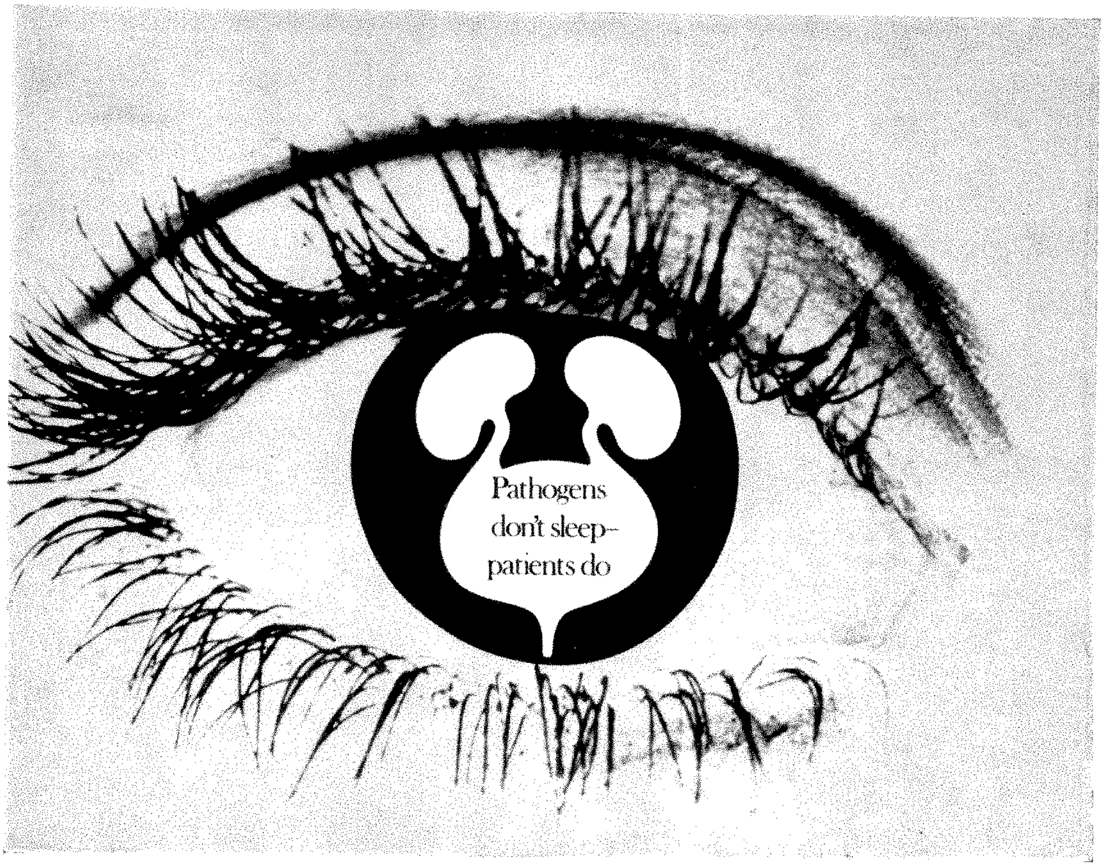

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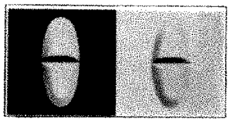

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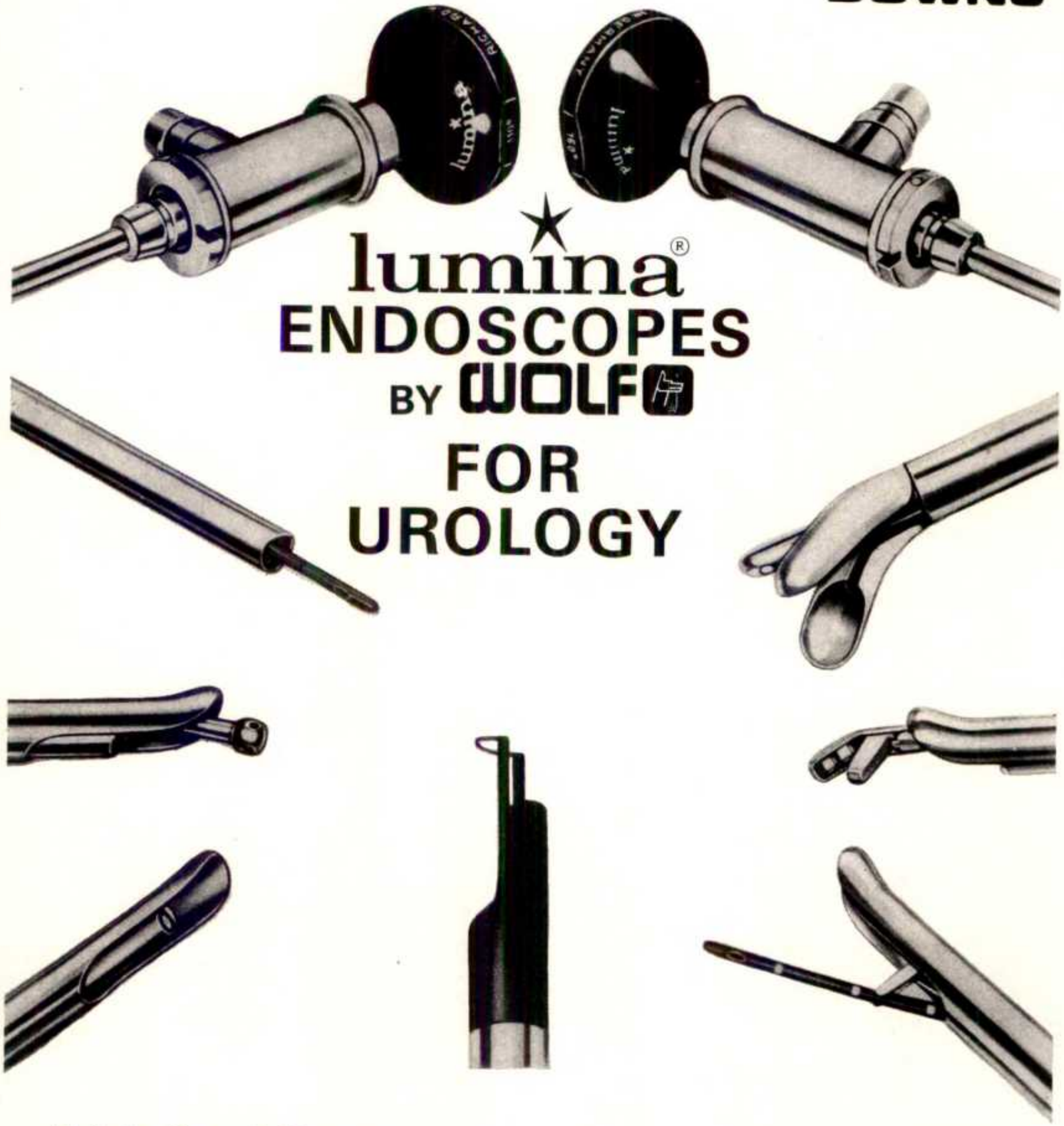

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[1] *J int med Res*, (1974), 2, 400

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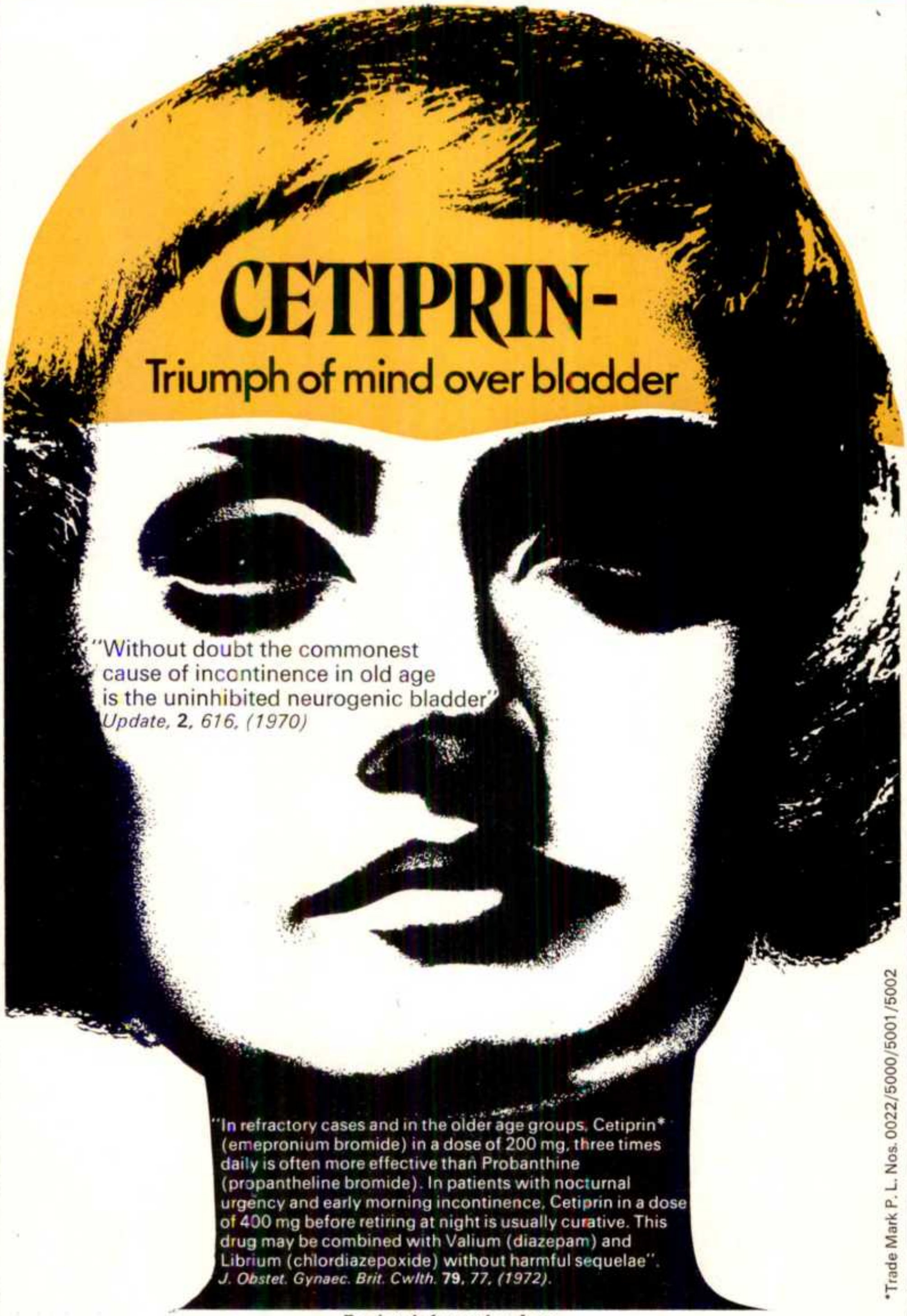
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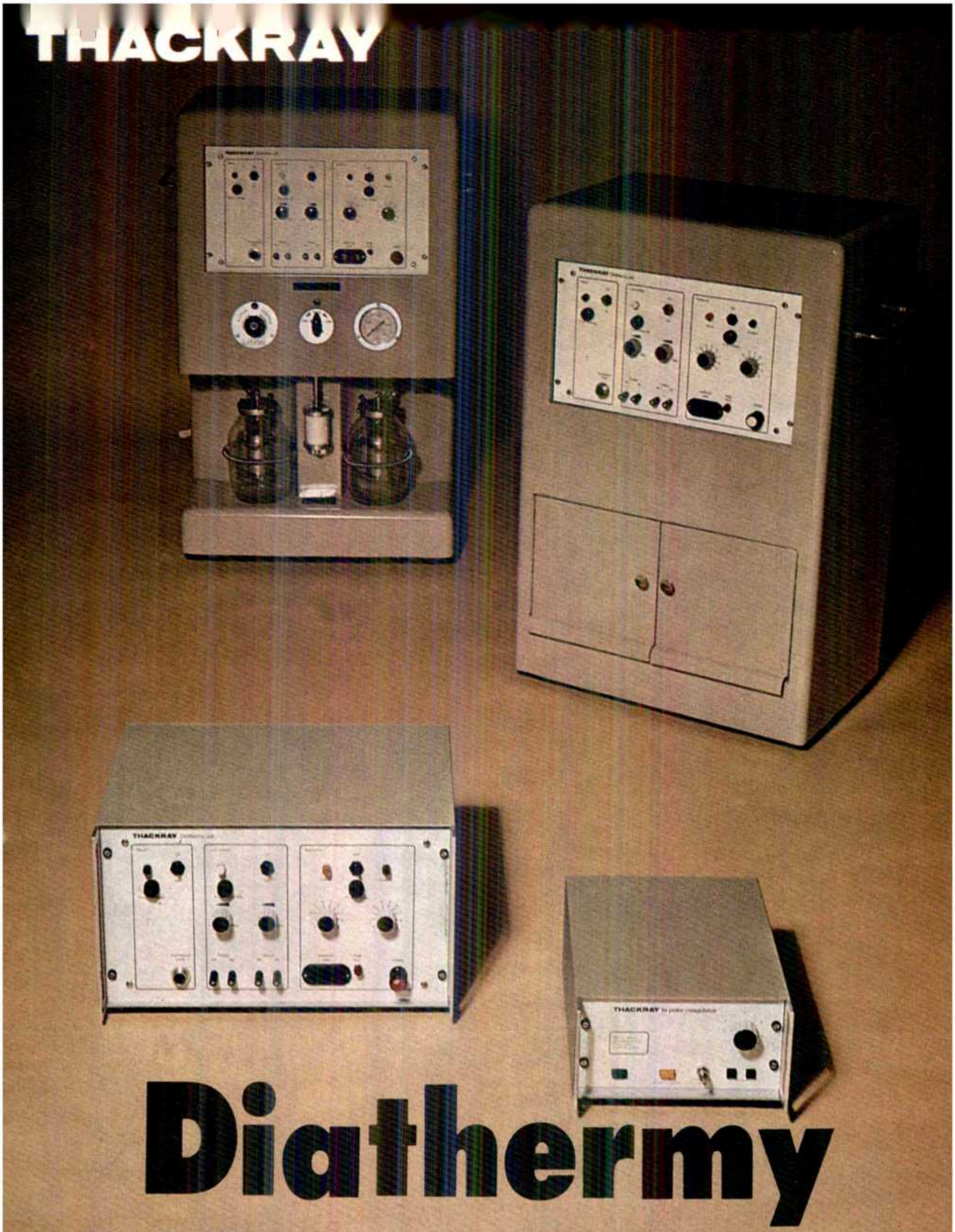

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When Amoxil was first introduced to the Medical Profession in May 1972 it was hailed as the successor to ampicillin. Since then research teams and clinical trial workers all over the world have reported that Amoxil is superior to ampicillin. Some of their reports have been in areas which were anticipated, but others have confirmed important superiorities which could not be predicted. These reports are obviously of considerable interest to the discerning clinician, and inevitably there have been many requests for a compendium of the available work. This is now available and will be sent upon request to interested clinicians. Brief summaries of the main areas considered in the compendium are given below.

More effective than ampicillin

There is evidence that Amoxil is more effective than ampicillin and this is particularly well illustrated in respiratory infections. Indeed, some reports have confirmed that Amoxil can succeed where ampicillin has failed[1,2,3]

Absorption unaffected by food

Early reports confirmed that Amoxil is twice as well absorbed as ampicillin, giving a peak serum concentration of 5.3 μg/ml[4] as opposed to ampicillin's 2.3 μg/ml[5]. Further work has shown that if both drugs are taken in the non-fasting state the overall absorption of Amoxil over the following 6 hour period is not significantly reduced, whereas that of ampicillin is reduced by nearly a third.

Amoxil's absorption characteristics mean that it is taken t.d.s. as opposed to ampicillin's q.d.s., and that the patient need not remember to take every dose in the fasting state.

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Studies at the Brompton Hospital[6] have shown that whereas ampicillin penetrates well into purulent sputum it penetrates very poorly into mucoid sputum. These workers have shown that Amoxil penetrates equally well into both purulent and mucoid sputum, and suggest that this may have far-reaching consequences in the treatment of respiratory infections.

Better tolerated

Although ampicillin is generally well tolerated, rashes and diarrhoea can be an irritating nuisance. A review of published literature indicates that Amoxil produces substantially less rash and diarrhoea than ampicillin.

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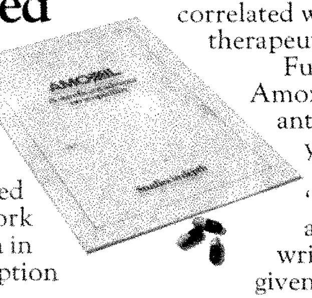

AMOXIL

Better than ampicillin in practice.

References: (1) Brit. J. Dis. Chest., (1972), 66, 185. (2) S.A. med. J., (1973), 47, 717. (3) Chemotherapy, (1973), 18, (Suppl.), 19. (4) Brit. med. J., (1972), 3, 13. (5) Antimicrobial Agents and Chemotherapy (1970), 438. (6) To be published (7) Antimicrobial Agents and Chemotherapy, (1970), 416.

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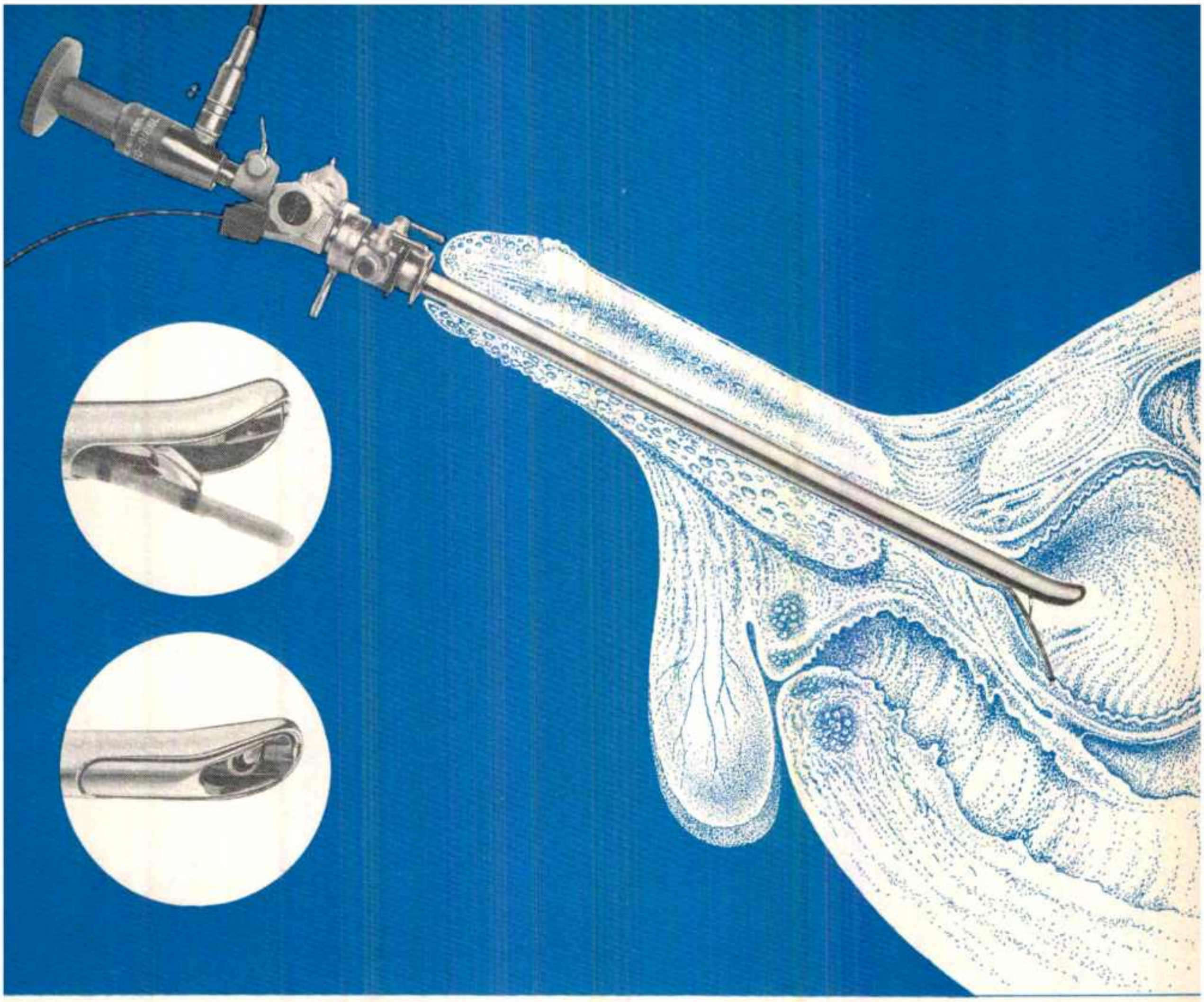

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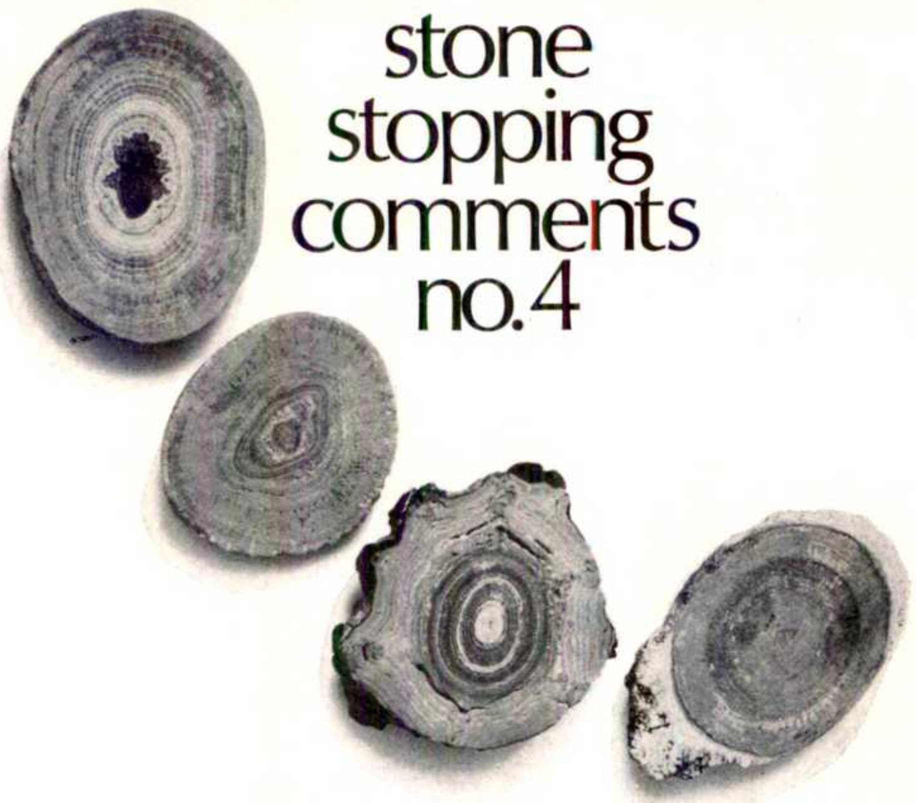

stone stopping comments no.4

In a recent study[1] measurements of ^{47}calcium and of urinary calcium excretion were made in 125 cases of urolithiasis (78 solitary stone, 47 recurrent).

The authors found that 57 out of 60 patients with hypercalciuria showed raised absorption of ^{47}Ca, whereas 49 out of 106 patients showing similar hyperabsorption of calcium had *normal* calcium excretion. The authors concluded that "... a majority of stone formers, whether they are hypercalciuric or not, absorb calcium excessively from the intestine and this is more prevalent in cases of recurrent urolithiasis."

As a sequel to investigation 1, the same authors[2] studied the effect of Sodium Cellulose Phosphate on intestinal calcium uptake. In comparison to a low calcium, low oxalate diet; "Sodium Cellulose Phosphate can significantly diminish the absorption of calcium from the intestine; there is concomitant diminution of urinary calcium excretion. The plasma levels of the divalent cations do not appear to be influenced by this therapy."

Dosage in this study was varied to evaluate therapeutic effect. "Five grams reduced the intestinal calcium by as much as 85% and even a 1 g dose resulted in a 50% reduction... Such a dose (5 g), however, is probably essential when it is considered that the substance will ordinarily be dispersed throughout a semi-solid food bolus." Optimum administration time was considered to be 5 g t.i.d. at meal times, or within 1 hour after food.

In terms of side-effects and toxicity, the authors stated "Serum levels of calcium and phosphorus were not altered in any of the patients even when the substance had been taken for a period as long as 7 years in a dose of 5 g 3 times daily." There was no diarrhoea or intestinal disturbance, and patients found SCP reasonably palatable and easy to take.

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1. Brit J Urol. (1974) **46**: 377-384.
2. Brit J Urol. (1974) **46**: 385-392.

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Urinary Lithiasis in Childhood in the Bristol Clinical Area

C. G. C. GACHES, I. R. S. GORDON, D. F. SHORE and J. B. M. ROBERTS
Bristol Royal Infirmary and Bristol Children's Hospital, Bristol

The recent literature has contained several papers on the subject of urolithiasis in childhood. Whether these communications have arisen from London (Ghazali, Barratt and Williams, 1973), the Netherlands (Scholten, Bakker and Cornil, 1973), South Africa (Du Preez and Cremin, 1973) or India (Aurora, Taneja and Gupta, 1970) all these series have contained material derived from a considerable area. The wide variations that occur in the types of urolithiasis on a geographical basis are now well established (Andersen, 1969). Lett, in 1936, showed that vesical calculi had virtually ceased to exist in England by about 1925 and it is still true to say that "stones in the bladder do not ingender oftener in children than in older folke" (after Barrough, 1617). We have undertaken a detailed study of our completely locally derived material in the particular hope that further light might be shed on this condition with regard to aetiological factors. The suspected rising incidence elsewhere of upper urinary tract calculi agrees with the findings of this Bristol series which is now discussed in greater detail.

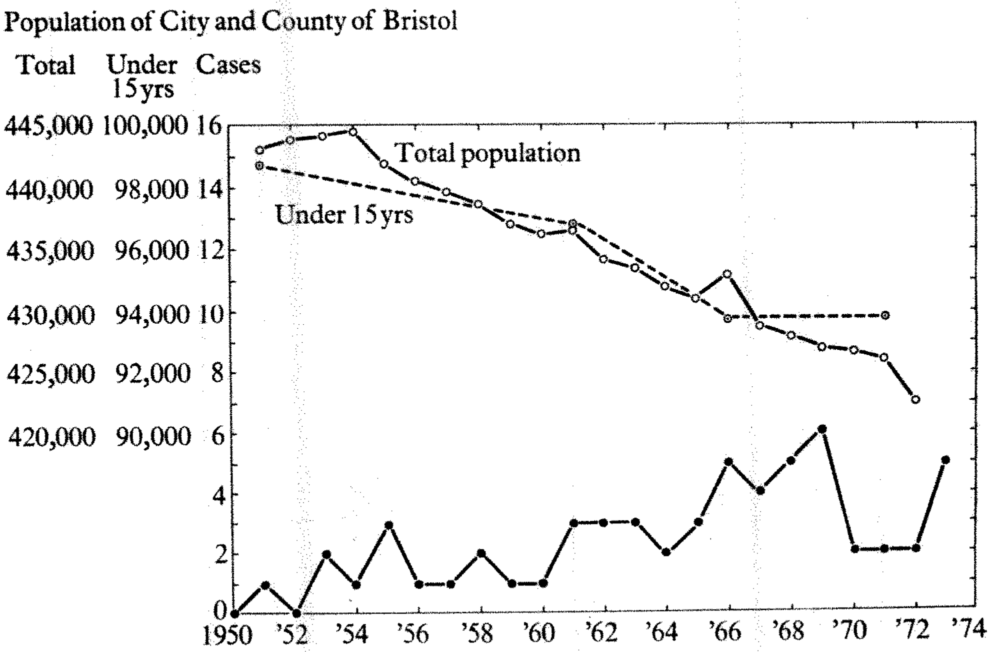

Fig. 1. Urinary lithiasis in childhood, Bristol 1950-1973.

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

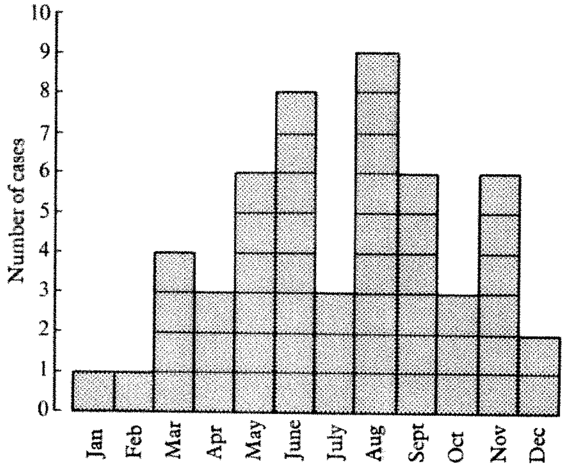

Fig. 2. Monthly case presentation graphs.

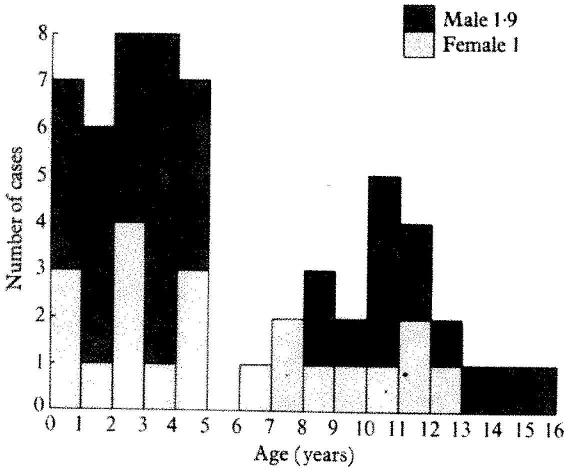

Fig. 3. Series age and sex distribution.

Patients

59 children presented in the period 1950-73, 65% of whom lived within the recently outdated City and County of Bristol boundary. The annual incidence of referral is shown in Figure 1 with the corresponding and almost linear fall in the city population which occurred during this period. It is worthy of note that the presentations of these patients reached a peak during the latter half of the summer months (Fig. 2). The significance of this association is discussed later. Our peak presentation at the age of 2 to 3 years agrees with that reported by Ghazali *et al.* (1973), but there is in addition a second smaller rising incidence maximal at the age of 10 years (Fig. 3). 61% of our cases were under the age of 5 years. The aetiological classification (Table I) indicates that we were able to reach a satisfactory conclusion that congenital anomalies (39%), metabolic disorders (8·5%) or primary infective processes (29%) were together associated with stone formation in 76·5% of cases. 22% had to be consigned to the idiopathic group, with no abnormality detected despite careful searching of clinical, radiological and biochemical evidence. Bristol has a smaller

Table I

Aetiological Classification

			Cases
Congenital:			23
1. Obstructive:	Pelvi-ureteric	10	
	Ureteric	2	
	Bladder neck	2	
	Urethral	0	
2. Other:	Horseshoe kidney	2	
	Hypoplastic kidney	2	
	Duplex system	2	
	Ectopic ureter	1	
	Spina bifida	2	
Metabolic:			5
Cystinuria		2	
Nephrocalcinosis: hyperparathyroidism		1	
Adrenogenital syndrome		1	
Purine metabolic disorder (leukaemia)		1	
Infective (alone)			17
Immobilisation			0
Foreign body			0
Stasis			0
Endemic			1
Idiopathic			13
			59

immigrant population than many other British cities, but the recent arrival of a child in this series together with his endemic bladder calculus derived in the Kashmir, suggests that there may again be a small upsurge of these cases in the United Kingdom.

Symptoms

Stone in the urinary tract is the cause of a wide range of symptoms ranging from general ill health to obvious signs of genito-urinary disease with urinary infection and haematuria (Table II). Haematuria was the commonest symptom and as in the older person this must be the prelude to a full urological investigation. It is interesting to note that below the age of 5 years, the presence of a renal or a ureteric calculus often gives rise to a central or vague abdominal pain. It is only above this age that the ability to lateralise the symptom appears to develop. Infection of the urine was detected in 58% of these children. A *Proteus* species alone was responsible in 25 patients with an emphasis on the particularly young. A mixed *Proteus* and coliform infection occurred in 3 and a coliform infection alone in 4 cases.

Radiological Findings

The differential diagnosis of a urinary calculus in children is usually not difficult, provided that the stone is detected either on the plain film or on excretion urography. Confusing opacities such as phleboliths, vascular calcification and gall-stones do not cause as much difficulty as in the adult. We have found oblique views to be extremely useful, particularly where the calculus overlies a bony structure and is itself not very radio-dense (Fig. 4, A and B). In the very young, even dense calculi can be completely overlooked if there are large amounts of gas and faecal

Table II

Presenting Symptoms

	Number of Patients	Percentage of Total
Haematuria	32	55
Abdominal pain (central or vague)	16	28
Fever	12	20
Vomiting	7	11
Loin pain or lateralised abdominal pain	6	10
Pain on micturition	4	7
Retention of urine	2	3
Failure to thrive	2	3
Frequency of micturition	1	1·5
Anorexia	1	1·5

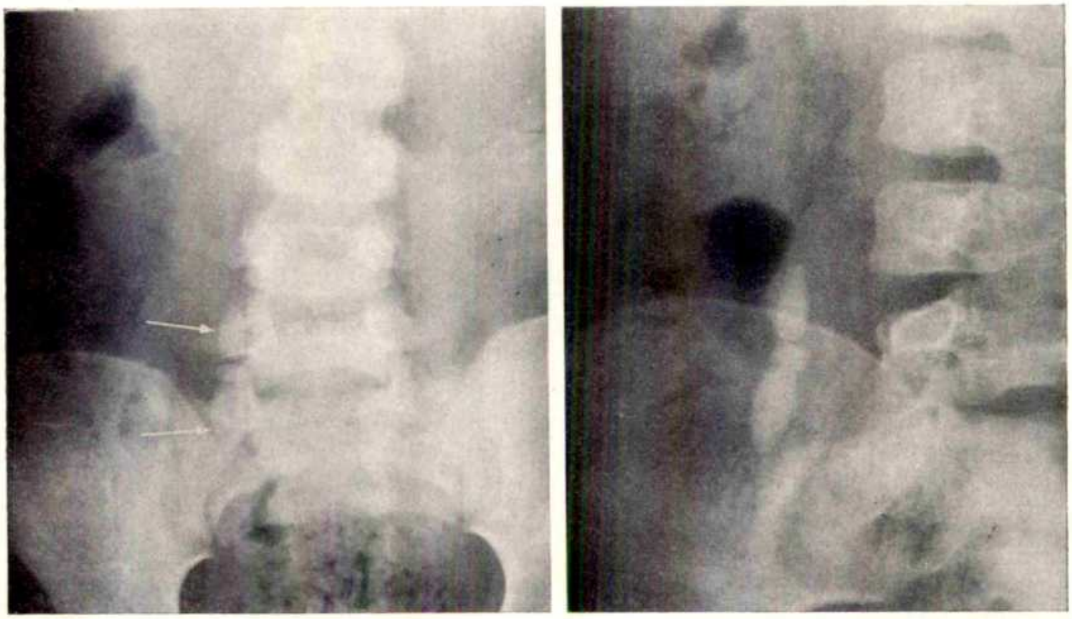

Fig. 4. The value of oblique radiographs where a calculus overlies a bony area. A, Cystine calculus arrowed. B, Left oblique presentation. P. K. Age 4 years.

material in the bowel. Tomography can be of great value in the localisation of renal calculi in particular (Fig. 5, A and B), and we would now regard such views mandatory in a similar situation. In this series, excretion urography was performed in all cases and was abnormal in 76% (Table III). Whilst hydronephrosis and hydroureter, as might be expected, were the commonest abnormalities, the low incidence of demonstrable scarring was most surprising. Of the 17% where the presence of congenital anomalies of the urinary tract were demonstrated, these appeared in most cases to be directly related to the calculi and were previously unsuspected. Occasionally, the excretory urogram will afford useful evidence of the presence of a calculus even when this has not been revealed on the plain radiograph. Non-opaque calculi were present in 4% of this series (Fig. 6).

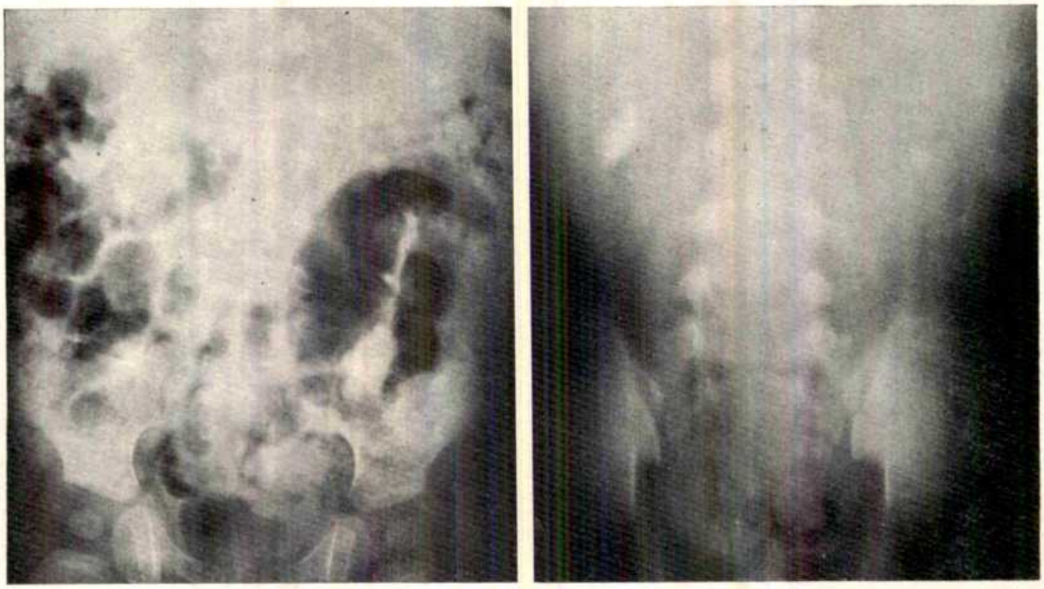

Fig. 5. The value of tomography in a baby to show additional unsuspected calculi. A, Left renal and urethral calculi only visualised on plain radiograph. B, Additional matrix calculus in right renal pelvis on tomogram. A. M. Age 3 months.

Table III

Radiological Findings

	Number of Patients	Percentage of Total
Normal	14	24
Hydronephrosis	19	33
Hydronephrosis + Hydroureter	10	17
Hydroureter	7	12
Renal scarring	1	2
Congenital anomaly	10	17
Delayed or diminished renal function	5	9
Trabeculated bladder	1	2

The anatomical localisation of these calculi is given in Figure 7. 30% of patients had more than one calculus, but in only 10% overall was the condition bilateral. A predominance in the lower elements of the kidney is again noted where an infected urine had been isolated. In the "non-infected" upper urinary tract there were surprisingly few calculi present in the kidney or the renal pelvis.

Treatment

In 17% of our children the calculus (or calculi) was passed spontaneously. In the remainder, surgical intervention was necessary (Table IV). During the operation of pyelolithotomy, which can be an extremely difficult and time consuming operation, particularly with matrix calculi, we would like to stress the value of endoscopy of the kidney. This manoeuvre has been of considerable value in 2 recent cases. The Dormia stone extractor has also a part to play in the older

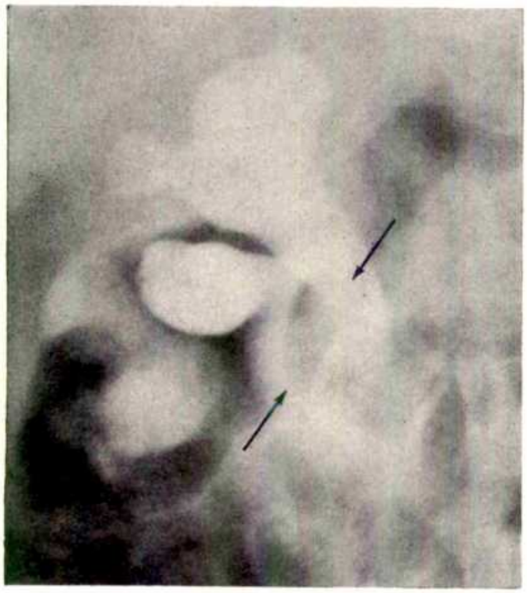

Fig. 6. Retrograde urography assisting in delineation of a completely non-opaque calculus. A. C. Age 3 years.

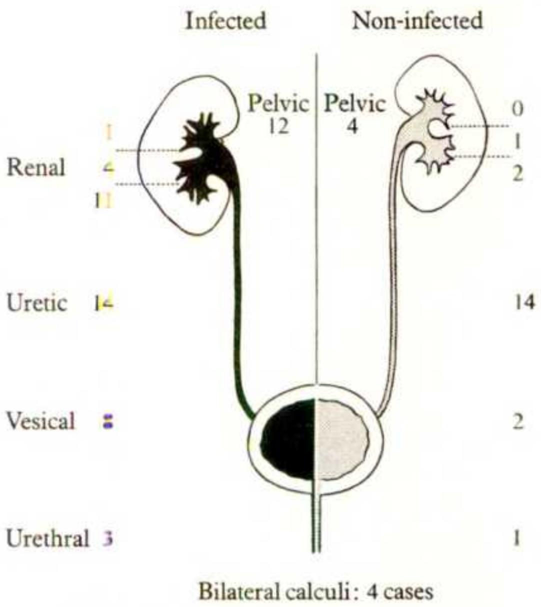

Fig 7. Anatomical distribution of calculi.

Table IV

Treatment Breakdown

	Cases
Voided spontaneously	10
Surgical removal:	
Nephrectomy	6
Partial nephrectomy	2
Nephrolithotomy	2
Pyelolithotomy	21
Ureterolithotomy	12
Dormia extraction	1
Litholapaxy	1
Lithotomy	7
Trans-urethral extraction	4

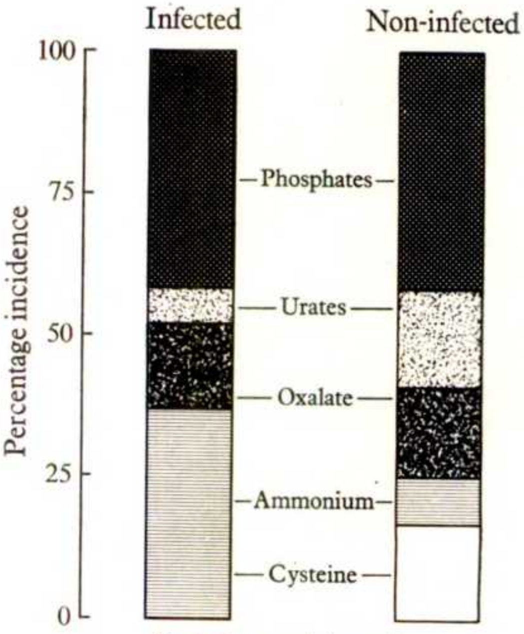

Fig. 8. Stone analysis results.

child. We have not so far found chemical analysis of the stone to be of great value. Analysis was completed in 60% of the stones removed (Fig. 8). We would add, however, that the presence of the ammonium radicle in the non-infected group suggests that we have failed to isolate a probable pre-existing urinary tract infection.

Results

We have been gratified with a low recurrence rate of 3·5%, excluding those patients with cystinuria (Table V). This level is similar to other recent experiences (Ghazali, Barratt and Williams, 1973). A recurrent stone problem was invariably associated with a *Proteus* infection. The importance of complete eradication of this organism, even in low concentration needs constant emphasis. We would hope that the existing higher standards in radiographic examination of the kidney at the time of surgery, combined with endoscopic examination of the renal pelvis, will eradicate the possibility of incomplete surgical removal.

Table V

Follow-up Results. Overall Recurrence Rate 7·0% (3·5% Cystinuria)
Unsatisfactory follow-up 8·5%.
Incomplete surgical removal 5·0%.

	Years after Primary Removal						
	1	2	3	4	5	Total	*Proteus* Infection
Overall recurrence	0	1	1	0	2	4	2
Renal calculi	0	1	0	0	2	3	2
Ureteric calculi	0	0	0	0	1	1	0
Vesical calculi	0	0	0	0	0	0	0
Urethral calculi	0	0	0	0	1	1	0

Table VI

Bristol Water Sources and Analyses. All Hardness Figures as Parts per Million

Source	Stowey	Barrow	Chelvey	Littleton	Carter Spring	Clevedon
Total hardness $CaCO_3$	134	200	206	213	356	365
Ca hardness $CaCO_3$	95	164	174	182	281	244
Mg hardness $CaCO_3$	39	36	32	31	75	121
Alkalinity as $CaCO_3$	77	169	281	113	305	297
pH	8·2	8·0	7·3	8·0	7·3	7·4
	3					
Patients	1	16	4	14	0	0

Epidemiological Study

With a series of patients which were derived locally, and which in addition belonged to a relatively fixed geographic group, we have looked into the analytical results of the 6 water sources which supply Bristol. The relevant findings are summarised in Table VI. In this area there is a threefold variation in the total hardness of the water as one moves from one part of the city to another (134 to 365 parts per million). We were surprised to find that the areas of great hardness (and which also have a significant proportion of young children) contained no examples of children's calculous disease. The greater proportion (79%) of these patients with stone formation were living in an area where the water was not only hard (200 to 213 p.p.m.) but also alkaline (pH > 8). Whilst we appreciate that our numbers are small, we consider that a wider survey would now yield valuable results and this has been initiated. We are also pursuing the water analysis data as it is our belief that there may be further substantial rises, over and above the mean values quoted, in both the calcium content and the pH values, maximal during the late spring and summer months. It has already been well demonstrated that hypercalciuria *per se* may not be so important as increase in urinary pH and oxalate ion concentration (Robertson and Nordin, 1968), and it is now suggested that the continuous daily intake of hard, alkaline drinking-water may possibly play a greater part in precipitating stone formation than has hitherto been recognised.

Summary

A series of 59 consecutive cases of urinary calculi in childhood is presented, being acquired from one local area (Bristol). These children were treated from 1950 to 1973. The peak presentation was in the 2nd and 3rd year of life, with a secondary peak in the 10th year. Anatomical (39%), metabolic (8·5%) or primary infective abnormalities (29%) were demonstrable, but 22% had to be left in an unsatisfactory "idiopathic classification". The overall recurrence rate of 7% was reduced to 3·5% when those patients with cystinuria were excluded. The local water supply areas have been studied and a tentative association is suggested between patients and their environment when they live in an area where the water is not only hard but also alkaline (pH > 8).

We would like to thank all our Bristol urological colleagues for their co-operation in this survey; the Medical Illustration Department of Bristol Royal Infirmary for the preparation of the photographs and Mr Gary James for the graphs and figures, and finally Miss A Kinghorn for preparation of the manuscript.

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The Natural History of Renal and Ureteric Calculi

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In 1967 a Stone Clinic was established at The London Hospital to study more intensively the many patients attending the Department of Urology with renal and ureteric stone disease. Many of these patients had already been followed up for a number of years, and others were added as patients were referred from time to time. We hoped to learn more about the natural history of stone disease; to establish the pattern of recurrence of these stones; to see what value studies of calcium metabolism might have in prediction of stone recurrence; and by investigating each patient fully, to attempt to define high and low risk groups. Study of the very large body of literature on calculous disease revealed very few investigations into patients who were not subjected to one or other form of treatment, and we thought it would be useful to attempt to build up a background picture of the natural history of this disease before embarking upon any trials of particular forms of therapy.

The Series (Table I)

The present series comprises 416 patients who were studied in the Stone Clinic from 1967 to 1971 inclusive. Not all patients with known calculous disease attending The London Hospital were necessarily referred to this clinic: in particular patients with other metabolic diseases such as hyperparathyroidism or cystinuria, who were already attending other clinics, were omitted from this study, as were some referred from other centres for operative treatment of staghorn calculi.

Each patient was subjected to a comprehensive urological and biochemical investigation including the usual studies of calcium metabolism, urography of the urinary tract, and renal function. All patients were followed by serial radiography, and entry to the present series was concluded at the end of 1971 so that all patients have been followed for at least 2 years.

Table I

The London Hospital Stone Clinic

	No. of patients	Mean length of follow-up (years)	No. of episodes
Male	243	7·7	392
Female	173	7·4	243

Table II

Aetiology of Stone Formation

	Male	Female
Anatomic abnormality	16	16
Recumbency	7	3
Hyperparathyroidism	2	2
Uric acid stone	3	0
Cystine	0	1
Bladder stone	4	0
Idiopathic	211	151
Total	243	173

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

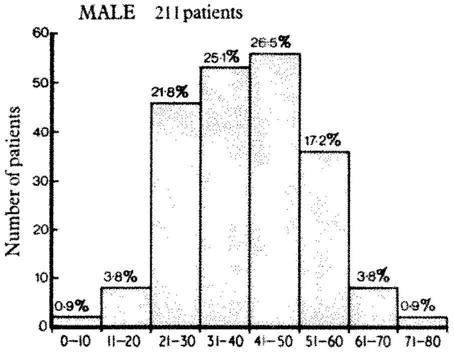

Fig. 1. Age at onset of symptoms.

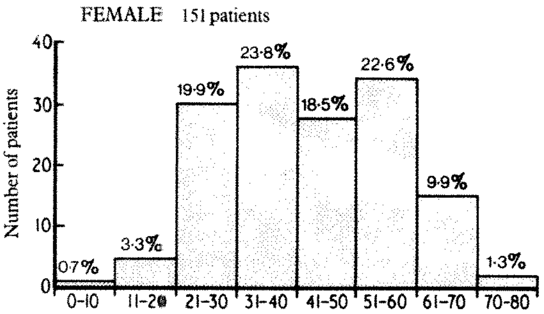

Fig. 2. Age at onset of symptoms.

In the course of the discussion we shall refer to stone "episodes": this term has been used to denote different things by different authors in the past. Here it means radiological evidence of a new calculus appearing in the urinary tract. The same stone whether observed or operated upon, and whether one or several operations was performed, is noted as amounting to one "episode".

During the course of the period of this review some patients were given thiazides, others phosphate, aluminium hydroxide, and low calcium diets. These patients have been excluded from the series, and did not amount to more than 10 cases in all.

Aetiology. Using the well-established criteria of stone aetiology (Williams, 1963) we found that in this series (Table II) there was a large proportion in whom no obvious cause could be found for the stone: in men this proportion was 86·6%, in women 87·2%. These "idiopathic" calculi occurred in 211 men and 151 women (362 patients altogether).

It is this group which forms the object of the present study. It should be noted that this proportion may be unduly large because patients with other obvious mechanical and metabolic causes for their stones may not have been referred to the Stone Clinic.

Age at onset of symptoms. We found that patients were fairly evenly distributed according to the age of onset of their first symptoms, throughout the middle decades from 20 to 60 years both in men and in women (Figs. 1 and 2), and we did not find the preponderance of younger men which had been reported in other studies (Williams, 1963; Sutherland, 1954).

Recurrence. During the period covered by this review 40·3% of the men developed a second calculus and 30·1% of the women. What was of consequence to the patient was the chance of his or her getting another stone in any particular year after the first one, and when this aspect was examined we found a very variable interval between the first and subsequent calculi both in men (Fig. 3) and in women (Fig. 4). A similar pattern emerged when the interval between the second and third stone was examined (Figs. 5 and 6).

Does the likelihood of getting another stone increase or diminish as the years go by? When the recurrence rate was calculated for each year after the first stone episode (Figs. 7 and 8) we found that the likelihood of a recurrence seemed to diminish slightly with succeeding years. The χ^2 test for trends on this data is significant for men at the 0·05% level, but the data for women are insufficient for this test of trends to be applied.

Hypercalciuria and recurrence of stone. The levels of 24 hour excretion of calcium in the urine are similar in this series to that reported in other series (Tables III and IV). But if we accept

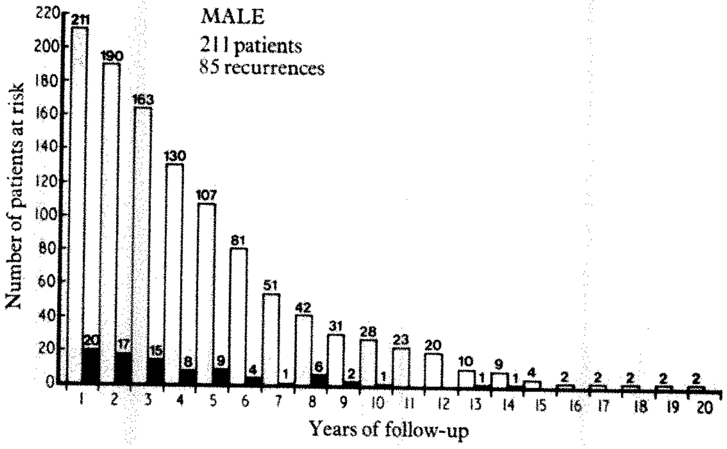

Fig. 3. Recurrence after first stone.

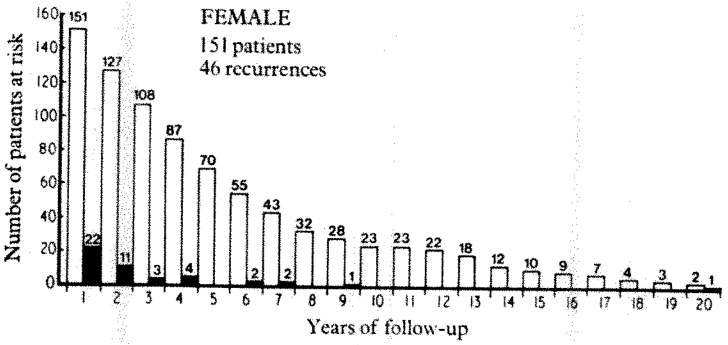

Fig. 4. Recurrence after first stone.

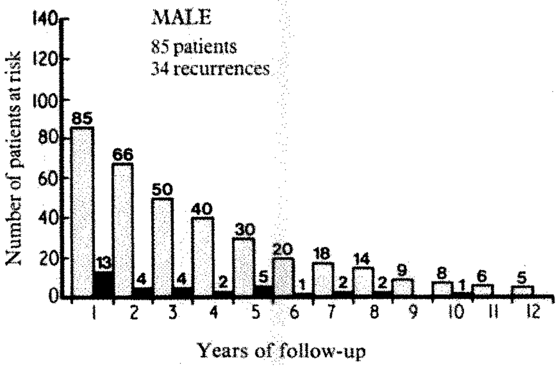

Fig. 5. Recurrence after second stone.

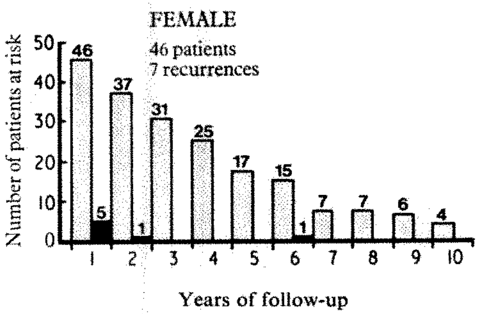

Fig. 6. Recurrence rate after second stone.

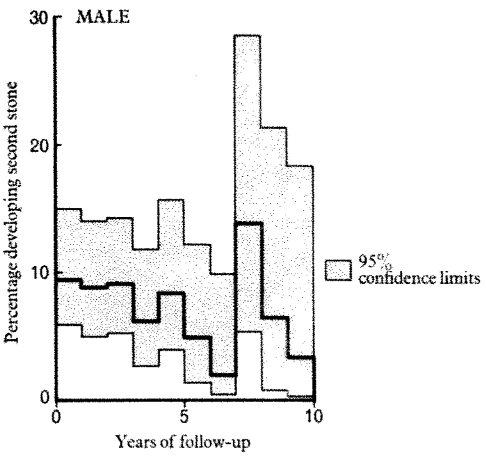

Fig. 7. % Developing second stone (male).

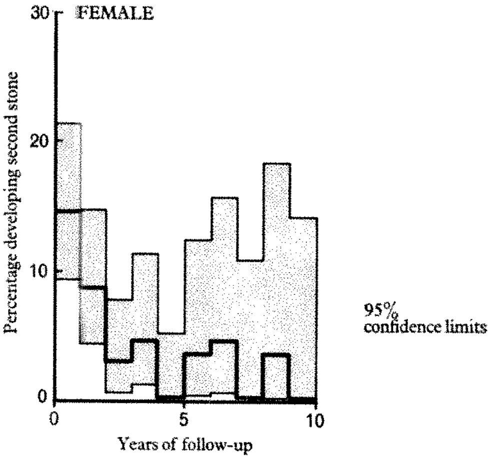

Fig. 8. % Developing second stone (female).

an upper limit of normal of 300 mg/24 hours for men, we find our incidence of hypercalciuria thus defined is almost double that which was reported from Leeds 15 years ago (Hodgkinson and Pyrah, 1958). For the present study we have chosen the 24 hour calcium excretion which was measured after the first calculus and before the second in the hope that this might be used to identify a group of patients who were particularly at risk to develop a recurrent stone. In the event we found the 24 hour excretion of calcium was only significantly higher in men who had at least 4 stone episodes. In those with 3 or fewer calculi there was no predictive value to be obtained from the measurement of urinary calcium excretion. Nor was there any similar trend in females no matter how many calculi they developed in the period under review (Figs. 9 and 10).

Infection and stone recurrence. We compared the recurrence rate between those who had infected urine and those who did not. By infection we meant that the patient had significant bacteriuria in two urine cultures after the first stone episode, and that the first infection had received appropriate antibiotic therapy: *i.e.* we were concerned with persistent rather than transient infection.

If an operation had been done then we took into account only those urine cultures which had been requested after the patient had been discharged from hospital.

Table III

Urinary Calcium Output (mg/24 hours)
(Measured after first episode but before second)

Male
8/211 no applicable measurement—203

Urinary calcium	No. of patients	% of total
<300	74	36·4
300-350	17	8·4
351-400	29	14·3
>400	83	40·9

Table IV

Urinary Calcium Output (mg/24 hours)
(Measured after first episode but before second)

Female
18/151 no applicable measurement—133

Urinary calcium	No. of patients	% of total
<250	67	50·4
250-300	27	20·3
>300	39	29·3

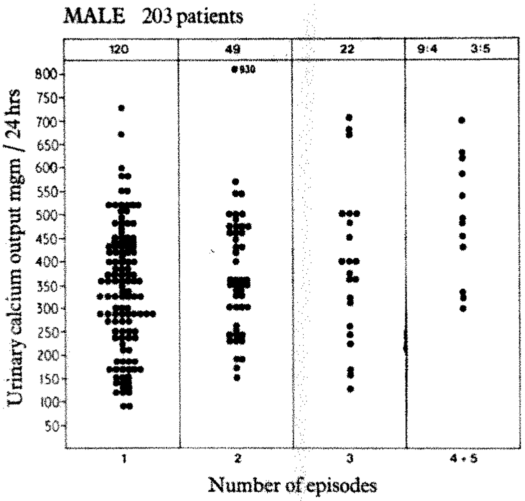

Fig. 9. Urinary calcium *v.* stone episodes.

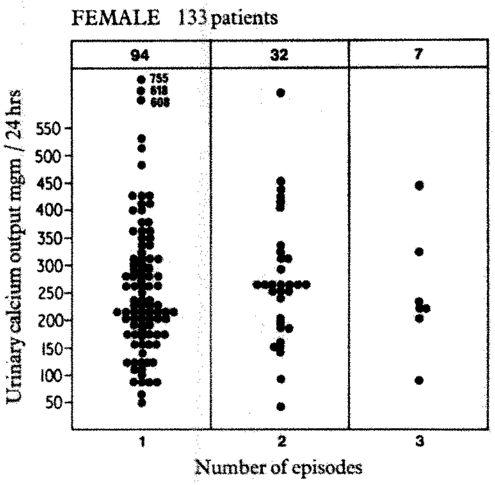

Fig. 10. Urinary calcium *v.* stone episodes.

Infection was found to be uncommon in males where only 9% were infected at any time, and only 6% remained infected after their first stone episode. Although the recurrence rate was higher in these men with persistent infection it was not significantly different from that in the uninfected patients (Table V). In contrast to these findings in men, there was a much higher incidence of infection among the women of whom 57·6% were infected at some time, and 47·7% had infection which persisted after their first calculus had been treated (Table VI). Among these women with persistent infection however the over-all recurrence rate was not significantly higher than in those without infection (Table VII, A versus B). If one considers the organism which was present, the recurrence rate was significantly and strikingly increased if the organism was *B. proteus*, or *B. proteus* with *Esch. coli* when compared with *Esch. coli* infection alone ($P < 0·01$, Table VIII).

Infection in combination with hypercalciuria. Whether we selected as the upper limit for urinary calcium excretion in women a figure of 250 or 300 mg per 24 hours, the combination of infection and hypercalciuria did not increase significantly the chance of stone recurrence (Table IX).

Table V

Infection and Stone Recurrence

Male

Infection 19/211—9%

Infected after first stone episode 14/211—6.6%

	No. of men	No. of recurrences	%
Not infected	197	77	39·1
Infected	14	8	57·1

$P > 0·05$

Table VI

Infection-Female

Not infected	64
Infected with first stone	15
Infected after first stone	33
Infected with and after first stone	39
87/151—57·6% infected at some time	
72/151—47·7% infected after first stone	

Table VII

Infection and Stone Recurrence

	No. of women	No. of recurrences	% recurrence
No infection	64	17	26·6
Infected with first stone	15	3	20·0
A	79	20	25·3
Subsequently infected	33	10	30·3
Infected with first stone and subsequently	39	16	41·0
B	72	26	36·1

A *v* B P>0·05

Table VIII

Infection and Stone Recurrence

Female—infection after first stone episode

Organism	No. of patients	No. of recurrences	% recurrence
E. coli	28	4	14·0
Proteus	23	13	56·5
E. coli and *Proteus*	14	7	50·0
Other organisms	7	2	28·5

Recurrence with *E. coli* infection significantly less (P<0·01) when compared with *Proteus* and also when compared with *E. coli* and *Proteus* (P<0·05).

Table IX

Infection, Calcium Excretion and Stone Recurrence

	Female		
	No. of patients	No. of recurrences	% recurrence
*Infection and calcium >300 mg/24 hrs	14	5	35·7
Infection and calcium <300 mg/24 hrs	48	14	29·2
No infection and calcium >300 mg/24 hrs	25	7	28·0
*No infection and calcium <300 mg/24 hrs	46	12	26·1

* No significant difference in recurrence rate ($P > 0·05$)

Discussion

This study shows again that long intervals can elapse between one stone and another, and that no patient can be regarded as having become free from the risk of a recurrent calculus even as long as 10 years after the first stone. In these patients, in whom the natural history of urinary lithiasis was only altered (if at all) by antibiotics, encouraging the patient to drink large volumes of water, and by the surgical removal of large and obstructing calculi, it is seen to be a recurrent process with an extremely variable and unpredictable course. 10 years after his first stone a man still has a 3% chance of getting another, with the 95% confidence limits ranging from 0·1% to 18·2%. Similar unpredictability was found among women, where the recurrence rate after 10 years could have been as high as 14%.

Despite finding a somewhat unexpectedly high incidence of hypercalciuria (49·6% in women, 63·6% in men) this did not seem to serve as a useful predictor of subsequent stone recurrence, except in the very small group of males in whom there were more than 4 or 5 stones during the period of observation.

It was also of interest to find that among the males, where one might have expected hypercalciuria to be most relevant, the recurrence rate gradually fell over the course of 10 years, even though no overt attempts were made in this group of patients to limit their excretion of calcium.

In the light of these findings we have become somewhat sceptical of those claims which are made from time to time that thiazides or other forms of treatment influence the recurrence rate of urinary calculi in any patients other than the small group of males with very frequent stone episodes. Any method of treatment which is aimed at lowering the level of urinary calcium excretion must be evaluated over a long period of time against a control group not so treated.

As for the significance of urinary infection, our findings point again to the importance of *B. proteus* as a factor in the recurrence of stones. We believe that perhaps some of the methods of selection employed in collecting this series, which excluded some women with staghorn calculi, would have emphasised even more the importance of *B. proteus* than these figures suggest. Other infections, notably those of the *Esch. coli* group emerge from this scrutiny as being of little consequence in the risk of stone recurrence, and the association of *Esch. coli* and hypercalciuria seems of equally little importance.

Where do we go from here? It seems that the immense labour which is currently exerted in urological departments to investigate calcium metabolism and to attempt to treat so-called hypercalciuria, may need to be reappraised in terms of its relevance to the management of the patient, and its cost effectiveness in terms of stone prevention. Any such appraisal must be set against the background of the natural history of stone disease. We are led to believe that much of our attention has been misdirected in our preoccupation with the concept of hypercalciuria, and that it might be more rewarding to turn our attention to other factors in the aetiology and clinical management of these patients such as the size of the calculi, their location within the architecture of the kidney, and the association of lithiasis with other renal disorders including hypertension. We hope to be able to report some of these other studies shortly, which may, we trust, shed further and perhaps more relevant illumination on the problem of the natural history of urinary lithiasis.

Summary

In a prolonged follow-up of a series of 416 patients at The London Hospital Stone Clinic it was found that recurrence could still occur even as long as 10 years after the first stone, though this risk decreased slowly year by year.

Recurrence is seldom related to hypercalciuria or urinary infection except when infection is caused by or associated with *B. proteus* in women.

Claims for the value of any form of therapy for stone disease must be evaluated against the background of the natural history of lithiasis.

We acknowledge the help we have had since the beginning of this work from Professor R. D. Cohen, Miss Rosemary Pask-Hughes, Bsc, and Mrs Helena Shaw, as well as the Endowment Funds and the Stone Clinic Research Fund of The London Hospital and Medical College.

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The Residual Renal Stone

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If it is true, as is so often said, that the least fragment of stone left behind in a kidney after operation will lead to a recurrence of the calculus, then many operations for stones in the kidney are a waste of time. This has not been our clinical experience: on the contrary, the improvement in the patient's symptoms, in the function of the kidney, and in the control of urinary infection more than outweigh the risk of recurrence of the stone. Moreover, recurrence of stone is not inevitable when a fragment has been left behind: nor does complete removal of a stone guarantee that a stone will not recur (Singh *et al.*, 1971, 1973). Experience gained in the course of operations on more than 120 large staghorn calculi over the course of 10 years has also made us sceptical as to the accuracy of complete clearance of a kidney, for we have often felt tiny particles of grit in the lining of the renal pelvis and calyces even when the preoperative radiograph appears to be clear, and biopsies of the kidney frequently show calcification in the renal parenchyma itself (Figure).

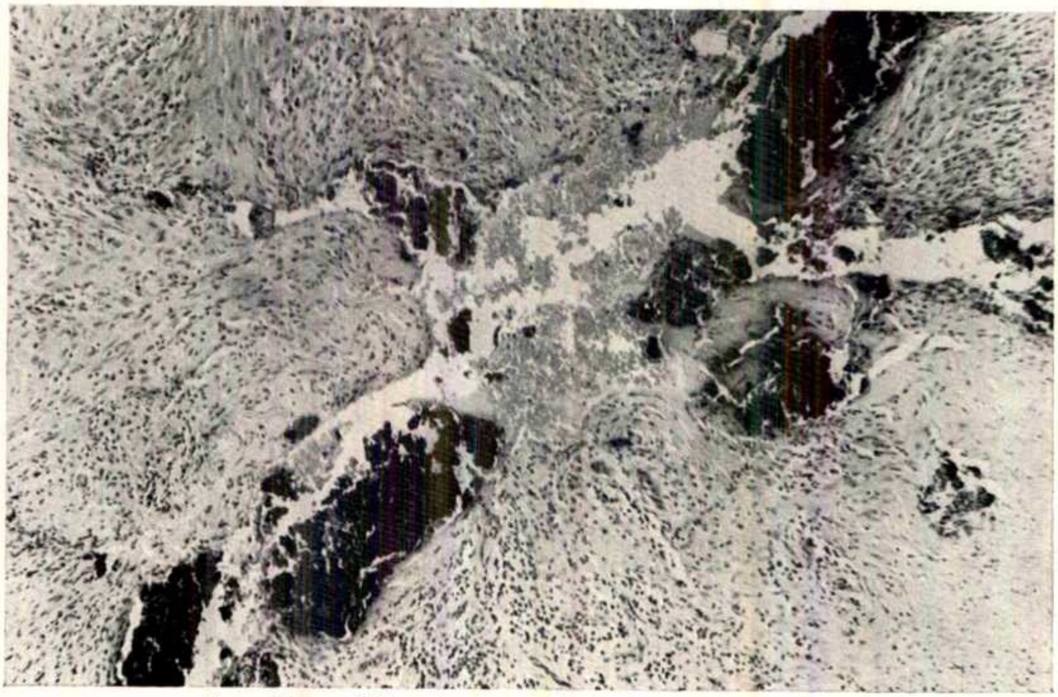

Figure. Biopsy of kidney showing calcification in the renal parenchyma.

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

We thought it would be useful to examine critically the accuracy and the range of observer error in interpretation of peroperative radiographs of the kidney, and then, armed with this information, to look again at what has happened to known fragments of stone left behind after operations for staghorn calculi.

Observer Error in Preoperative Radiographs of the Kidney

Method

Small measured pieces from a staghorn calculus (mixed calcium magnesium phosphate and carbonate) were placed in a cadaver kidney and X-rayed. The pieces were of various sizes: the small ones were 1 × 1 mm, the larger ones 2 × 3 mm and 2 × 2 mm as measured with a micrometer screw gauge. They were placed within the kidney in 14 different combinations which were accurately charted and recorded, and X-rays were made using 2 different exposures (70 Kv 100 mA 0·3 sec and 65 Kv 100 mA 0·25 sec). The film used was the standard Kodak "kidney" contact film used in peroperative radiography. The resulting 28 films were shown to 6 experienced observers (4 surgeons and 2 radiologists) all well-used to looking at these films. The radiographs were read in a random order, and each observer marked the position and size of the calculi on a blank sheet bearing the outline and calyceal pattern of 28 kidneys.

Table I

X-ray Readings
28 X-rays per person (76 stones in 28 X-rays)

Observer	No. of X-rays read correctly	No. of X-rays stones missed	No. of X-rays false positive
1	16	9	3
2	16	9	3
3	8	11	9
4	12	10	6
5	14	9	5
6	8	18	2
	74 (44%)	66 (39·2%)	28 (16)

Table II

Total Number of Stones

1. Available for diagnosis to 6 observers	6 × 76 = 456
2. Size distribution	
A—3 × 2 mm	
2 × 2	
2 × 1	264
B—1 × 1 mm	192
Total	456

Results

Each observer was shown 28 films, and so 168 observations were recorded. Only 44% of the observations were correct. In 39·3% of the X-rays stones were missed and stones which were not there were marked down in 16% (Table I).

Since 76 stones altogether had been "seeded" in the 28 films, the observers should have detected 76 × 6 = 456 stones (Table II). In fact they missed 104 stones—all but one of them being the small 1 × 1 mm particles (Table III). Only 37·3% of these 1 × 1 mm particles were correctly detected, but when the calculi were larger (2 × 2 or 2 × 3 mm) 99·5% of them were correctly detected. (The difference is statistically significant $P < 0{\cdot}002$.)

Because the observer error was so great when the particles were small, it was possible to look at only the observations in the larger calculi to consider how correctly they had been positioned: 79·6% of them were located correctly.

There was no significant difference in the correctness of observations when the two different X-ray exposures were compared, nor when the first 14 observations of each observer were compared with the last.

This study clearly shows that the conventional radiographic diagnosis of small calculi is only accurate when the particles are larger than 1 mm in diameter, even in the ideal circumstances of this test. In the less favourable conditions of the operating theatre, when the films are often less correctly positioned and exposed, the accuracy is likely to be even worse. Particles 1 mm or smaller in diameter are very likely to go undetected.

The Fate of the Residual Fragment of Stone

Over the last 10 years 120 large branched staghorn calculi have been removed from 100 patients, 20 of them with bilateral stones (Table IV). As judged by peroperative contact X-rays and the

Table III

Number of Stones Missed

Category			
A	2 × 1 mm and bigger	1/192	*0·005%
B	1 × 1 mm	103/264	*39·4%
	Total	104/456	= 22·8%

* Difference between A and B is statistically significant $P < 0{\cdot}002$.

Table IV

Extended Pyelolithotomy
for Staghorn Calculi
the London Hospital 1964-74

	Patients	Kidneys
Unilateral	80	80
Bilateral	20	40
Total	100	120

postoperative films there was an incomplete removal of stone in 29 kidneys (24·4%). In 6 kidneys the particles were 1 × 1 mm or less in diameter: in the other 23 the fragments were larger than 2 mm across (Table V).

Residual Calculi

In the 6 kidneys with the small particles less than 1 mm across, no change was seen in the follow-up period in 5 of them, and 1 of the kidneys became cleared entirely (as judged by successive radiographs over the years) (Table VI).

In the 23 kidneys with the larger fragments there were 8 in whom the original removal had been particularly difficult, and larger and often multiple fragments had been left behind: these were the only fragments which could be seen to act as the nucleus for subsequent new stone growth. 5 of the 23 incompletely cleared kidneys subsequently got rid of the fragments which had been left behind. In 9 kidneys the residual fragments remained quite unchanged but it was interesting to note that in 2 of these 9 kidneys a new calculus formed elsewhere in the kidney but not on the original residual fragment.

Table V

Staghorn Calculi—Completeness of Removal

Complete removal	91 kidneys (75·6%)
Incomplete removal	29 kidneys (24·4%)
Fragments bigger than 2 × 2 mm	23 kidneys
Dust measuring 1 × 1 mm or less	6 kidneys

Table VI

Fate of Kidneys Incompletely Cleared

23 kidneys with fragments	8 regrowth	(34·7%)
	*10 unchanged	(43·4%)
	5 passed	(21·9%)
6 kidneys with dust	1 cleared	No recurrence of stone
	5 unchanged	

* In 2 kidneys the fragments remained unchanged but there was new stone formation.

Bilateral Staghorn Calculi

These 20 patients form an interesting group. In 12 patients both kidneys were completely cleared, and have remained clear during the period of the follow up. In 8 patients only 1 of the pair of kidneys was completely cleared, so that 1 kidney acts as a control for the other. Of the 8 kidneys which were completely cleared, 4 developed a recurrent calculus, 1 became non-functioning, and 3 have kept clear of recurrent stone during the period of review. Of the 8 kidneys which were not completely cleared 7 developed a new stone, and in 1 the residual fragments did not grow. In the entire group of 40 kidneys 29 of them either remained clear, or the residual fragment did not grow. It should be added that few of the recurrent stones grew to be staghorn calculi.

Discussion

It seems very likely that many of those kidneys which we thought were completely cleared of stone did in fact harbour tiny particles of a size which would have gone undetected by peroperative contact radiographs. Even if we could improve the radiographic technique still further, there would still be innumerable tiny foci of calcification in the renal parenchyma and collecting ducts which could act as the nidus for further stone formation. In practice our follow-up suggests that it is by no means disastrous to leave tiny fragments behind, even though it is obviously desirable to get them all out. New stones did not always form on residual fragments, and when new stones did form, it was not always on these fragments acting as nuclei. These results fully support the conventional view that it is advisable to take every reasonable precaution so as to remove calculi as completely as possible, and that leaving large bits behind is apt to be followed by a recurrence of stone. But they do not support the idea that it is futile to attempt to remove a stone unless that removal can be complete. Removing the stone does not cure the patient of stone disease, and the surgeon who sets out to remove a calculus should temper his zeal with some understanding of the natural history of the disease and the limitations of his ability to detect residual calculi.

Summary

A study of the observer error built in to contact preoperative radiography for renal stones shows that particles less than 2 mm in diameter are likely to be missed.

The radiographic follow-up of 100 patients from whom 120 large staghorn calculi have been removed over a period of up to 10 years shows that new calculi may form in kidneys which have been completely cleared, and that residual stones do not always grow, but equally often pass spontaneously, or remain unchanged.

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Calculus Pyonephrosis with Candida Albicans Infection

Case Report

An otherwise fit, nondiabetic woman aged 41 presented with a pyonephrosis due to a pure growth of *Candida albicans*, above a recurrent stone, impacted at the pelviureteric junction. Following pyelolithotomy the kidney was drained by a nephrostomy but the pyrexia failed to resolve and *Candida albicans* was repeatedly grown in the nephrostomy urine. After 8 days a course of 5-fluorocytosine (5-FC) was commenced and blood and urinary drug levels with sensitivity assays demonstrated adequate concentrations. A very rapid resolution of the pyrexia (Fig.) was followed by the eradication of candida from the urine. Follow-up showed one *E. coli* infection, but no return of the candida. Ureteric reflux was absent.

Comment

This patient had a superficial candida infection of the kidney with sparing of the renal parenchyma. Such an infection is very unusual in the absence of diabetes or an impaired immune response. Oral 5-FC, unlike amphotericin B, is well concentrated in the urine and is not known to cause marrow or liver damage, (Davies and Reeves, 1971). Although candidal resistance to 5-FC has been reported (Shadomy, 1969), it is recommended as the drug of choice provided urinary concentrations and organism sensitivities are monitored.

We would like to thank Dr R. R. Davies of the Department of Microbiology, St Mary's Hospital, for carrying out the bacteriology and for his advice on the management of this patient, and also Professor J. P. Blandy under whose care the patient was admitted.

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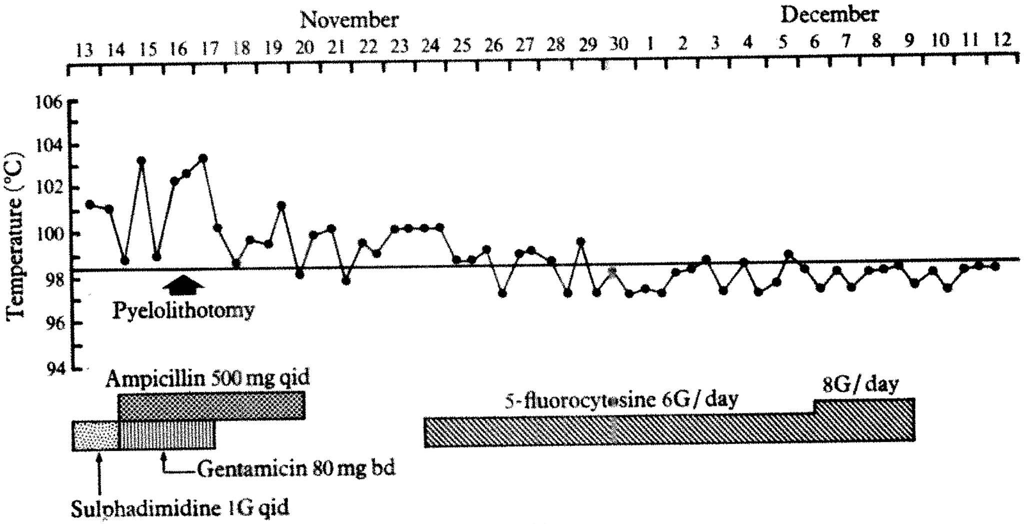

British Journal of Urology (1975), **47**, 131–135

Some Data on Urinary Stones which were Passed

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During the last few years, we have analysed collections of urinary stones from many centres by the X-ray powder method (Lonsdale, Sutor and Wooley, 1968), and recently, the results of this work and any available data on the stones and patients have been coded and stored in an IBM360/65 computer (Sutor, Wooley and Illingworth, 1974). In the case of the collections from Northern Ireland, Eire, South Africa and many from Great Britain, information was provided on whether the stones were removed surgically or passed. It was therefore possible to compare the composition and other data for stones which had been passed with the same parameters for all stones from these countries, to find if any significant differences existed between the 2 groups.

Method

For each patient in the collections for which information was provided on whether or not the stone had been passed, the following information was also usually available—age, sex, any previous history of stone disease, number of stones obtained, their weight, composition and site in the urinary tract when diagnosed. The transference of these data on to computer cards has been described in a previous paper (Sutor *et al.*, 1974). In the case of recurrent stone-formers, if more than one episode occurred during the period when the calculi were collected, information relating to these episodes was combined on one card so that the group of recurrent stone-formers is composed of different people. The computer programs used for handling and analysing the data and testing statistical significance were the ones described in the earlier paper. Only 2 age groups were considered—patients under 50 years and those 50 years and over, and the number of stones formed was classified as single or multiple (2 or more). Because of the small number of calculi which had been passed, subdivision of the data could only be made for a few variables at a time.

Results

Out of the 979 patients comprising the whole collection, 175 passed the stone(s) analysed. The sex, age, previous history of the disease, the number of stones obtained and their site when diagnosed in the urinary tract for all patients and for those who passed stones are shown in Table I. Compared with the whole group of stone-formers, there are, among the patients who expelled calculi, significantly more males than females ($P<0{\cdot}001$), significantly more people in the younger age group than in the older one ($P<0{\cdot}001$), significantly more recurrent stone-formers than those having no previous history ($P<0{\cdot}001$) and only just significantly more single than multiple stones ($P<0{\cdot}05$). Most of the calculi expelled apparently came from a kidney or ureter and the ratio of stones from these sites is the same as the ratio of kidney and ureteric stones in the whole collection. However, very few expelled calculi were in a bladder when first diagnosed and the proportion of these bladder calculi among stones passed is significantly less than their proportion in the whole group ($P<0{\cdot}001$).

Table I

Comparison of the sex, age, any previous stone history the number of stones obtained and their site when diagnosed in the urinary tract for patients who had passed their stones and for those in the whole collection

	Whole collection	"Passed" stones	Statistical significance
Sex			
Males	637	139	$P<0{\cdot}001$
Females	335	35	
Age (years)			
2-49	535	129	$P<0{\cdot}001$
50-81	420	40	
Previous history			
Yes	243	65	$P<0{\cdot}001$
No	369	41	
Number of stones			
1	653	139	$P<0{\cdot}05$
2 or more	170	21	
(fragments only)	156	15	
Site			
Kidney	479	98	Not significant
Ureter	298	67	
Bladder	171	5	

Table II

Distribution of stones among the different composition types

Composition type	Whole collection	"Passed" stones
F	70	7
C	255	88
F+G	187	10
C+F	317	61
C+F+G	46	1
B+F+G	17	—
Others	87	8
Total	979	175

Key to symbols: B = ammonium acid urate, C = calcium oxalate, F = calcium phosphate, G = struvite.

The stones were divided into groups according to their overall composition (Sutor *et al.*, 1974) and their distributions in these for the whole collection and for the stones which were passed are shown in Table II. The 2 distributions are significantly different and among the stones which were passed there are significantly more pure calcium oxalate calculi or type C ($P<0{\cdot}001$) and significantly less of the calcium phosphate+struvite (F+G) and calcium oxalate +calcium phosphate+struvite (C+F+G) varieties ($P<0{\cdot}001$ and $P<0{\cdot}05$ respectively), but there are no significant differences in the number of pure calcium phosphate stones (type F) or

Table III

The effect of site, sex and age on the distribution of stones among the 4 main composition groups
(Key to composition symbols as for Table II)

Site/sex/age	Whole collection	"Passed" stones	Whole collection	"Passed" stones
	F stones		*C stones*	
Kidney	23	3	115	48
Ureter	18	2	118	38
	F+G stones		*C+F stones*	
Kidney	114	4	153	37
Ureter	34	5	111	20
	F stones		*C stones*	
Females	21	1	51	11
Males	49	6	204	77
	F+G stones		*C+F stones*	
Females	113	7	89	13
Males	74	3	228	48
	F stones		*C stones*	
2-49 years	32	4	144	65
50-81 years	38	3	104	21
	F+G stones		*C+F stones*	
2-49 years	118	9	174	46
50-81 years	70	1	136	12
	F stones		*C stones*	
Males aged 2-49	18	3	122	59
Males aged 50-81	30	3	77	17
	F+G stones		*C+F stones*	
Males aged 2-49	39	3	119	39
Males aged 50-81	35	—	104	8

calcium oxalate+calcium phosphate ones (C+F). Stones composed of pure calcium oxalate and calcium oxalate+calcium phosphate which are the most frequently occurring composition types in technically-developed countries have respectively a 1 in 3 and a 1 in 5 chance of being passed but, for an infection stone consisting of calcium phosphate+struvite, the chance is only 1 in 19, and 1 in 25 for all infection types (F+G, C+F+G and B+F+G) grouped together. If the composition varieties are subdivided according to the patient's sex, the same trends are observed.

Stones in each of the 4 main composition types, (C, C+F, F, F+G) were then divided according to their site when diagnosed and the patient's age and sex (Table III) and the ones which had been passed were compared with those in the whole collection. This showed that in each composition group, kidney and ureteric calculi are just as likely to be passed except in the case of the F+G or infection variety in which significantly more "passed" calculi came from the ureters. Also for each composition type, males and females have the same chance of passing a stone. In most cases there is a higher proportion of males who passed stones, but the differences between the sexes are not significant probably because of the small number of female cases involved. Patients in the younger age group are more likely to pass a pure calcium oxalate stone ($P<0{\cdot}01$) and a calcium oxalate+calcium phosphate one ($P<0{\cdot}001$) than those in the older group, but the calcium phosphate and calcium phosphate+struvite varieties are just as likely to be passed by patients in both age groups. When the composition types are divided according to both the age and sex of the patient the same is true. Males in the younger group are more likely than those in the older one to pass calcium oxalate stones ($P<0{\cdot}05$) and calcium oxalate+calcium

Table IV

Classification of the calculi according to weight, and the percentage of stones passed in each group
(When necessary, weights were rounded off so they were within the limits specified below)

Weight (g)	All stones	"Passed" stones	Percentage of stones passed
≦0·009	17	13	76·5
0·01-0·09	242	117	48·3
0·1-0·9	398	44	11·1
1·0-9·0	233	0	0
10·0-99·0	77	0	0
≧100	1	0	0
Unweighed fragments	11	1	—

Table V

Average weight (g) of all stones and those which were passed in the different composition groups for both female and male patients
(Key to composition symbols in Table II)

Composition type	Females		Males	
	Whole collection	"Passed" stones	Whole collection	"Passed" stones
F	2·63	0·20	3·39	0·07
C	0·60	0·08	0·62	0·05
F+G	6·43	0·27	5·97	0·36
C+F	1·28	0·13	1·76	0·11
C+F+G	5·38	0·20	9·42	—
B+F+G	6·21	—	20·74	—

phosphate ones ($P<0·001$) and the chance of this occurring is 1 in 2 and 1 in 3 respectively. A similar trend is shown by females but the numbers are too small for the differences to be significant.

The stones which were passed range in weight from 0·001 to 0·80 g and the heaviest one has dimensions of 1·5 × 0·8 × 0·7 cm and belongs to the C+F composition group. The proportion of "passed" stones in the calculi grouped according to their weight is shown in Table IV. The highest percentage (76·5) is for the stones weighing under 0·01 g. A comparison of the average weights of the different composition varieties for calculi which had been passed and for all those in the group is given in Table V for both male and female patients. The average weights of expelled stones are, as expected, much less than those of all the stones but, rather surprisingly, since all stones must nucleate and grow, they vary with the composition type. The relationship between the weight and composition of a calculus which is evident here and which has been discussed in a previous paper (Sutor *et al.*, 1974) is also found in stones which were expelled from the urinary tract, and the trends are similar in both groups for both sexes.

Summary

Out of a group of 979 patients with urinary calculi, 175 had passed their stone(s). Comparison of data for stones which had been passed with data for the whole group shows many significant differences.

Calculi composed entirely of calcium oxalate are more likely to be expelled than any other composition variety. The chance of this happening is 1 in 3 and it is even higher when the person is under 50 years of age. The probability of calculi composed of calcium oxalate + calcium phosphate being expelled is 1 in 5 and this also increases for younger patients. Infection stones consisting of calcium phosphate + struvite have only a 1 in 19 chance of being passed.

Many of the stones passed (130) are under 0·10 g in weight. However, there is a similar relationship between composition and weight among both the stones that were passed and the whole group. In both groups, pure oxalate stones are the lightest, infection stones are the heaviest and stones composed of calcium phosphate and calcium phosphate + calcium oxalate are of intermediate weight.

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Adrenal Cyst associated with Hypertension

Adrenal cyst is a rare but surgically important condition. Up to 1966 about 220 adrenal cysts had been reported (Foster, 1966). So far only 5 adrenal cysts associated with hypertension have been described (Gigax *et al.*, 1972).

Case Report

A 38-year-old female was referred with a diagnosis of hypertension probably of renal origin. On examination she was found to have a diastolic pressure ranging from 110 to 120 mm of Hg and grade II hypertensive retinopathy. Abdominal examination revealed a mass in the left loin, measuring 6×4 inches with all the physical findings of a kidney mass.

All routine urine and haematological investigations were within normal limits. Serum creatinine, electrolytes, urinary 17 ketosteroids, 17 hydroxycorticosterone, VMA, and catecholamine levels were within normal limits. Regitine test was borderline positive on 2 occasions. Histamine provocation test was negative. EKG showed left ventricular strain. Chest X-ray revealed slight unfolding of the aorta. Plain X-ray KUB region was essentially normal. Excretory urogram revealed good bilateral kidney function and marked downward displacement of the left kidney, probably due to a mass in the left adrenal gland Aortography and selective left renal angiogram revealed normal vascular pattern of the left kidney with markedly depressed main renal and upper polar vessels. There was evidence of a relatively avascular space-occupying lesion in the left adrenal with blood vessels skirting around its border. (Fig.)

The left adrenal was explored and a massive adrenal cyst was removed. The gross specimen measured 15×10 cm, with an irregular bosselated surface. The cut section showed multilocular cyst filled with clear and haemorrhagic fluid. The microscopic picture showed hamartomatous cyst of the adrenal.

The postoperative period was uneventful, and the diastolic blood pressure returned to 90 mm Hg within 2 months.

Comment

5 groups of adrenal cysts are recognised (Abeshouse, Goldstein and Abeshouse, 1959): parasitic cysts, epithelial cysts, endothelial cysts, angiomatous cysts and pseudocysts. Cystic hamartomas are mainly composed of lymphangiectasia with varying amount of angiectasis.

Symptomatic and palpable adrenal cysts should be removed surgically to alleviate symptoms and to prevent complications like haemorrhage, infection and hypertension. These cysts can usually be dissected easily and removed without injury to the kidney.

We could not find any obvious reason for the production of hypertension in this case. Pressure upon the kidney tissue and its vasculature and the angulation of the renal vessels produced by the large, expanding, adrenal cyst, is probably a factor in the production of hypertension.

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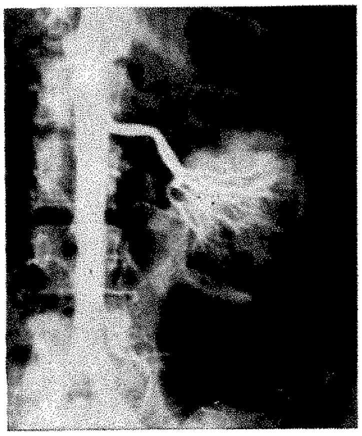

Fig. Selective left renal angiogram showing relatively avascular space occupying lesion of the left adrenal pushing the kidney and its vasculature downwards.

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Hypertension and Renal Artery Stenosis with Aneurysm Formation in a Solitary Kidney in a Patient with Neurofibromatosis

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Hypertension due to renal artery neurofibromatosis is rare and only 16 cases have been reported (Allan and Davies, 1970; Smith *et al.*, 1970; Bourke and Gatenby, 1971). In these, stenosis of the main renal artery near its origin has occurred and, where histological examination has been carried out, neurofibromatous tissue has often been demonstrated in the stenosed area (Allan and Davies, 1970). Distal to this, aneurysmal dilatation of the artery frequently occurs. Conservative management of non-calcified renal artery aneurysms is reported to have a 25% mortality from rupture of the aneurysm and a further 10% require nephrectomy for uncontrollable haematuria (Smith and Hinman, 1967). Calcified aneurysms are less likely to rupture, but only if their diameter is less than 1·5 cm can they safely be left untreated (Poutasse, 1966). Reconstructive operations have a high failure rate (Ekeström, 1964; Clunie *et al.*, 1971), and the control of renovascular hypertension by nephrectomy has been disappointing (Smith *et al.*, 1970). Renal artery stenosis and aneurysm formation occurring in patients with solitary kidneys is extremely rare and only 5 other cases have been reported, none with neurofibromatosis (Mathé, 1948; Harrow and Sloane, 1959; Slaney, Ashton and Dawson-Edwards, 1964; McKiel, Graf and Callahan, 1966; Oschner and Busch, 1969).

We wish to report a case of renal artery stenosis and aneurysm occurring in a patient with hypertension, neurofibromatosis and a solitary kidney, treated by renal artery reconstruction. Measurements of plasma renin activity were related to body sodium content and arterial blood pressure and the findings discussed with reference to previous animal studies in which one renal artery had been occluded and the other kidney removed. An operative procedure is described in which the kidney was perfused in situ. This was found to be an acceptable alternative to removal of the kidney before arterial reconstruction and autotransplantation.

Case Report

History

The patient, a man aged 27, presented at The London Hospital in April 1970. He had frequent headaches during childhood, but otherwise had been perfectly well until he was admitted to another hospital in 1964 following a motor cycle accident, when his blood pressure was found to be 240/120 mm Hg. His hypertension was not investigated or treated. In April 1970 he underwent a routine medical examination and his blood pressure was found to be 180/120 mm Hg. He was referred to The London Hospital for investigation. His father, aged 58, had angina; his mother, aged 56, had neurofibromatosis and also had angina. One brother and one sister, and one of his sons, aged 3½, also had neurofibromatosis.

Examination

He was small (height 158 cm, weight 57·8 kg) with generalised pigmentation. There was wasting of the left temporalis muscle, probably the result of neurofibromatosis. There were numerous café-au-lait patches and neurofibromata scattered over the trunk and limbs. In the chest he had mid-systolic and early diastolic murmurs, and his blood pressure was 200/135 mm Hg (lying) and 180/120 mm Hg (standing). Peripheral pulses were all present and equal.

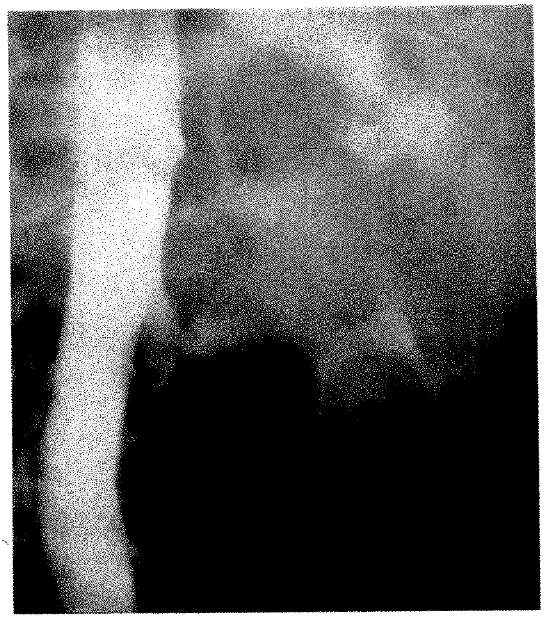
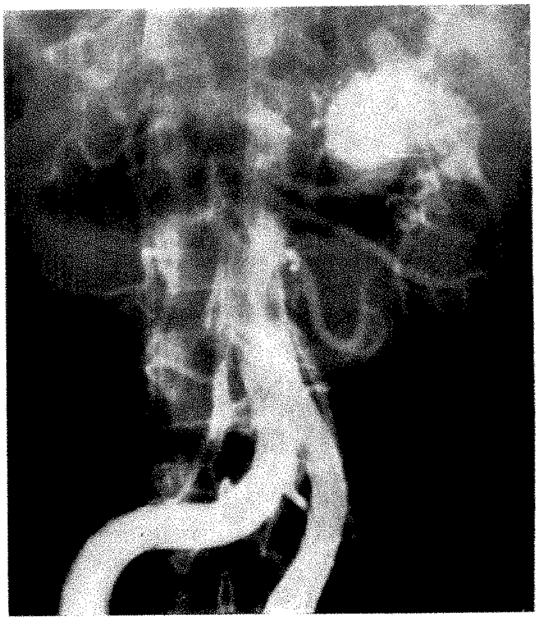

Fig. 1. Preoperative renal arteriogram showing stenosis of the left renal artery.

Fig. 2. Preoperative renal arteriogram showing a multilocular aneurysm distal to the stenosis.

There was a continuous bruit, maximal at the end of systole, but extending into diastole, over the entire abdomen, heard best in the left upper quadrant and loin. The optic fundi showed arterial narrowing but were otherwise normal. Routine urine analysis was normal.

Investigations

A full blood count, sedimentation rate, and plasma electrolyte, urea and creatinine concentrations were all within normal limits. His urine was sterile and 24-hour urinary excretion of V.M.A. normal on numerous occasions. An E.C.G. showed left ventricular hypertrophy.

A chest X-ray showed cardiac enlargement and aortic unfolding. A plain X-ray of the abdomen demonstrated a ring of calcification partially overlying the medial portion of the left renal shadow. Tomography confirmed that the calcification lay in the plane of the kidney. No renal shadow could be identified on the right. Excretion urography showed no evidence of excretion of contrast on the right. The left kidney measured 15·1 cm in length and showed normal excretion of contrast which outlined a normal pelvi-calyceal system and bladder. Renal arteriography (Figs. 1 and 2) showed a stenosis of the left renal artery approximately 1 cm from its origin with a multi-locular aneurysm beyond, the proximal part of which corresponded to the ring shadow seen on the plain film. The aneurysm appeared to involve the proximal intra-renal branches. The more peripheral renal branches were not demonstrated owing to retention of contrast within the aneurysm. There was no renal artery on the right.

Volume and Renin Studies

During arteriography samples of blood were collected simultaneously from the aorta, the left renal vein and from the inferior vena cava below the entry of the renal vein. Plasma renin activity was measured by the method of Newton and Laragh (1968). The results are shown in Table I and demonstrate an appreciable arterio-venous gradient for renin across the left kidney.

After the patient had received a constant diet containing 103 mEq of sodium daily for 5 days, plasma volume, extracellular fluid volume (sulphate space) and exchangeable sodium were measured simultaneously by isotope dilution, using ^{131}I-labelled human serum albumin (5 μCi)), $Na_2{}^{35}SO_4$ (50 μCi) and ^{24}NaCl (100 μCi) respectively. The method has been described in more detail elsewhere (Dathan, Johnson and Goodwin, 1973). Peripheral venous blood was collected for plasma renin activity at 12 noon, the patient having been out of bed for more than 3 hours.

Figure 3 shows the state of sodium balance (faecal sodium was not measured), plasma renin activity and blood pressure, taken at 9.00 a.m. each morning with the patient recumbent, throughout the study. In Table 2 are shown the results of the body fluid compartment measurements, performed on days 5 to 6. Plasma volume, exchangeable sodium and extracellular fluid volume were each higher than the mean value plus one standard deviation for normal subjects, expressed as a function of body weight. Expressed another way, as a function of height^3, plasma volume

Table I

Plasma Renin Activity of Samples taken during Renal Arteriography

	Plasma Renin Activity (ng/ml/hr)
Aorta	3·1
Inferior vena cava	3·3
Left renal vein	5·0

Table II

Plasma Volume, Exchangeable Sodium and Extracellular Fluid Volume Measurements.

Weight 57·8 Kg Height 158 cm

	Absolute	per kg B.W.	per m³
Plasma volume (ml)	2681	46·4 (39·4 ± 4·7)*	688·0 (570 ± 110)*
Exchangeable sodium (mEq)	3168	54·8 (41·4 ± 5·2)**	812·5 (546 ± 55)**
Extracellular fluid volume (ml)	13300	230 (165·5 ± 17·6)*	3410 (3440 ± 780)*

* Mean values ± l.S.D. for normal subjects, calculated from the data of Albert *et al.* (1968).

** Mean values ± l.S.D. for normal subjects, calculated from the data of Forbes and Perley (1951).

and exchangeable sodium were each considerably raised above normal, while extracellular fluid volume fell within the normal range. Plasma renin activity was 1·1 ng angiotensin II/ml plasma/hr of incubation. The range for normal subjects receiving a daily dietary sodium intake of between 80 and 120 mEq is 0·5 to 2·0 ng/ml/hr (Newton and Laragh, 1968).

The patient was then given a low sodium diet (19 mEq sodium daily) and 5 days later, when sodium balance had been achieved (Fig. 3) plasma renin activity was 2·1 ng/ml/hr, a level which was not significantly raised above the range for normal subjects receiving a liberal intake of sodium. Thus the normal rise in plasma renin activity which occurs in normal subjects in response to dietary sodium deprivation (Brown *et al.*, 1963) appeared to be absent or blunted.

Finally, he was given a ward diet with no restriction of sodium, and a week later Bethanidine 10 mg t.d.s. was prescribed. Further measurements of plasma renin activity both before and during treatment with Bethanidine (Fig. 3) were essentially within the range found in normal subjects receiving a daily dietary sodium intake of between 80 and 120 mEq.

Treatment

At operation, the absence of the right kidney was confirmed. On the left side, arising just distal to an area of stenosis, was a multilocular aneurysm of the main trunk of the renal artery from which arose all the main branches of the artery. After placing a curved arterial clamp on the aorta, the main trunk of the renal artery was detached, leaving the renal vein and ureter intact. The renal artery was then cannulated and perfused with an ice-cold solution of 1·4% sodium bicarbonate and 10% laevulose, followed by a solution of Dextran 40 in an electrolyte solution (Perfudex) (Brunius *et al.*, 1968). The perfusate was allowed to escape into the general circulation via the renal vein without detectable variation in the E.C.G. or blood pressure. Perfusion was continued until the kidney was uniformly blanched and cold to touch. Reconstruction of the artery was then carried out by arterioplasty (Fig. 4), the majority of the aneurysmal wall being removed and the remainder being reconstructed around an 8 ch rubber catheter to form an artery and branches of normal calibre. After excision of the stenosed segment, the main trunk was then reanastomosed to the aorta. The total ischaemic time was 90 minutes. Within a few minutes of restoration of the circulation to the kidney, urine excretion began and continued without interruption thereafter.

Histological examination of the vascular tissue removed showed non-specific intimal thickening and fibrosis, but no neurofibromatous tissue was demonstrated.

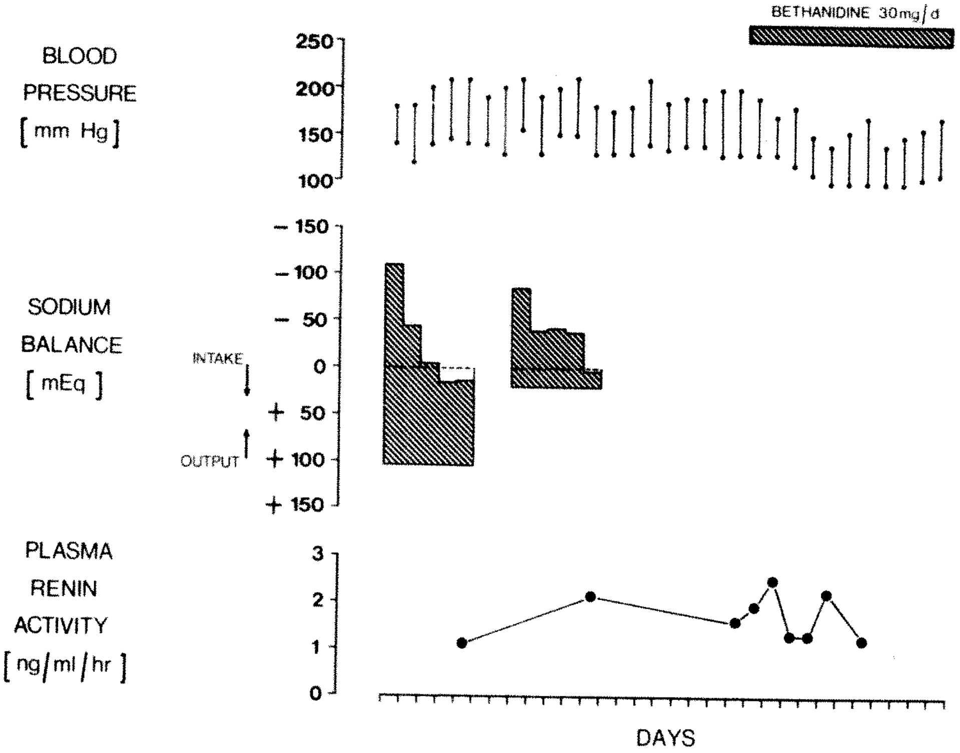

Fig. 3. The effect of changes in sodium intake and hypotensive therapy on blood pressure and plasma renin activity.

Postoperative Course

The patient's postoperative course was uneventful. However, he remained hypertensive, and required hypotensive therapy. Renal arteriography was repeated (Fig. 5) and showed only slight narrowing of the left renal artery close to its origin from the aorta and a little dilatation of the proximal intra-renal branches. The more peripheral arterial branches filled well and without the delay encountered pre-operatively. 5 months later he felt well and was taking 30 mg guanethidine daily. His blood pressure was 160/115 mm Hg (lying) and 130/80 mm Hg (standing). Plasma renin activity was 1·5 ng/ml/hr with a concurrent urinary sodium excretion of 89 mEq/day. His renal function remained normal.

Discussion

Sodium, Renin and their Relationship to Hypertension

In attempting to define the pathogenesis of renovascular hypertension, two factors, body sodium content and renin, and their relationship to arterial pressure have been studied in detail in both the experimental animal and man. In animals with chronic hypertension produced by renal artery constriction and contralateral nephrectomy, renal and plasma renin concentrations are normal (Regoli *et al.*, 1962; Gross, Regoli and Schaechtelin, 1963; Brown *et al.*, 1966; Bianchi, Tilde Tenconi and Lucca, 1970). With the contralateral kidney intact however, plasma renin concentration is increased (Schaechtelin, Regoli and Gross, 1963), although many patients with unilateral renal artery stenosis and hypertension still have a plasma renin concentration which is within the normal range (Brown *et al.*, 1965). Bianchi *et al.* (1970) demonstrated that in these patients plasma volume and extracellular fluid volume, both dependent on body sodium content, were significantly greater than in patients with essential hypertension: in patients with a raised

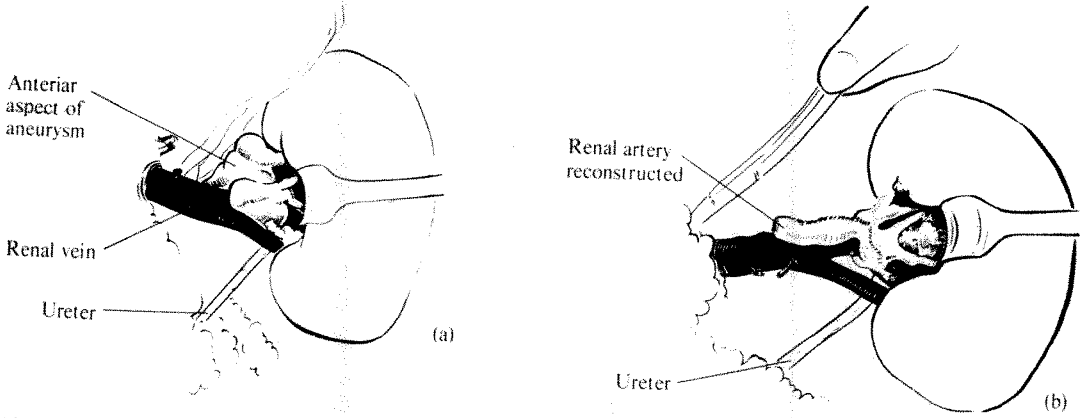

Fig. 4. Anterior view of the aneurysm at operation: (*a*) before and (*b*) after arterial reconstruction.

plasma renin concentration, plasma volume and extracellular fluid volume were not significantly elevated. There appears therefore to be an interaction between the volumes of those fluid compartments which reflect body sodium content and the level of plasma renin, and in renovascular hypertension the mechanism whereby the blood pressure becomes elevated may depend in some way upon an increase in either or both of these factors. Ledingham (1971*a*) has suggested that the hypertension associated with chronic renal failure may in some cases be due to renin secretion which is inappropriate for the sodium status of the individual. A similar situation may exist in patients with renovascular hypertension.

The measurements of plasma renin activity, exchangeable sodium, plasma volume and extracellular fluid volume in the patient reported are of great interest and support the evidence obtained elsewhere in animals and man. The finding of a normal plasma renin activity is in agreement with observations made in animals with renovascular hypertension produced by unilateral renal artery constriction and contralateral nephrectomy. Although the level of plasma renin activity after a period of normal sodium intake (approximately 100 mEq/day) was within the normal range found in normotensive subjects, this level may in fact have been inappropriately high for the expanded fluid volumes and increased body sodium which existed at the time. The means by which such an expansion of plasma and extracellular fluid volumes leads to an elevation of the blood pressure is uncertain and has been fully discussed by Ledingham (1971*b*).

The failure of plasma renin activity to rise in response to a low sodium intake, as in normal subjects (Brown *et al.*, 1963), is in accord with the findings of Miksche, Miksche and Gross (1970) who found that in rats made hypertensive by unilateral renal artery constriction and contralateral nephrectomy, plasma renin activity was also unaffected by dietary sodium restriction. This failure of renin release to respond to the stimulus of sodium deprivation may be related to the increased body sodium which appears to result from the removal of the opposite unclipped kidney (Tobian, Coffee and McCrea, 1969).

In the rat with chronic hypertension produced by unilateral renal artery constriction and contralateral nephrectomy, removal of the constriction results in a prompt and permanent fall in blood pressure to normal within 24 hours (Byrom and Dodson, 1949). The failure of the patient's blood pressure to fall to normal may have been due to the presence of some residual renal ischaemia caused by a minor degree of stenosis either in the reconstructed main renal artery or in one or more of its main branches which were involved in the reconstructive procedure. Alternatively it may have been the result of undetected neurofibromatous lesions affecting the smaller vessels within the renal parenchyma (Bourke and Gatenby, 1971; Reubi, 1945).

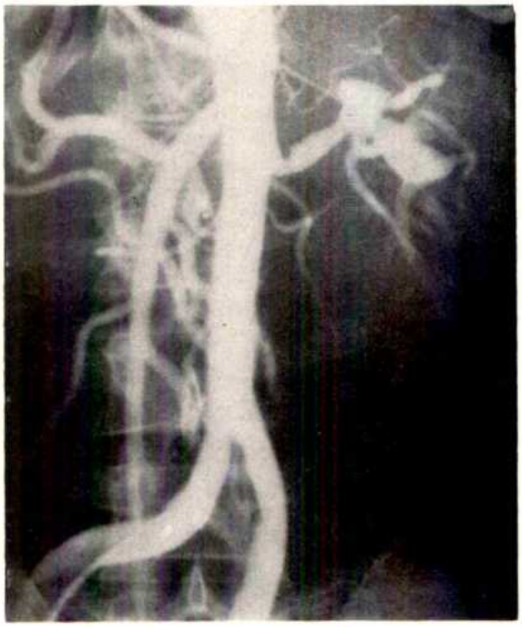

Fig. 5. Postoperative renal arteriogram.

Surgical Aspects

Conservative management of renal artery aneurysms may result in thrombosis of the aneurysm (Eastcott, 1969) or retroperitoneal rupture, a complication with a mortality of approximately 75% (Harrow and Sloane, 1959), and in this case absence of the other kidney precluded nephrectomy. Reconstruction of the artery was therefore undertaken, despite the indifferent results previously reported for this form of treatment (Ekeström, 1964; Smith and Hinman, 1967; Cerny, Chang and Fry, 1968). The pathological anatomy here precluded the more conventional method of reconstruction by excision and graft replacement, and, although total removal, repair and autotransplantation of the affected kidney has been carried out by several workers (Calne, 1971), reconstruction of the artery *in situ* by arterioplasty seemed preferable and more convenient. The use of cooling, by total body hypothermia (Semb, 1956; Birkeland *et al.*, 1959; Slaney *et al.*, 1964) or by local perfusion cooling methods (Eadie *et al.*, 1965), has been shown to protect the kidney from the effects of ischaemia for at least two hours, and a similar technique for perfusion cooling of cadaveric kidneys has been used successfully for some time (Brunius *et al.*, 1968). The method of *in situ* local cooling used here achieved a satisfactory reconstruction of the artery and excellent return of function, without disturbance of the vein or ureter or any systemic upset to the patient. Accordingly it is suggested that the application of this technique to other cases of renal artery anomaly, even where both kidneys are present, might improve the success of arterial reconstructive operations and allow more extensive and complicated procedures to be undertaken.

Summary

A case of hypertension in a patient with neurofibromatosis and renal artery stenosis with aneurysm formation in a solitary kidney is described.

Studies of plasma renin activity and body sodium content are presented and have been related to findings in patients and experimental animals with renovascular hypertension.

A reconstructive operative procedure is described in which the kidney is perfused *in situ*.

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Atraumatic Rupture of the Kidney

A Case Report with Autopsy

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A comprehensive review of the literature on atraumatic rupture of the kidney by Joachim and Becker appeared in 1965. Spontaneous bleeding from gross lesions in the kidney (secondary haemorrhage) make up the bulk of reports, while reports of spontaneous haemorrhage from "healthy" renal tissue (primary haemorrhage) are very rare and often of doubtful validity (see Table). The present case belongs to this latter group. The condition is difficult to diagnose pre-operatively and treatment is open to discussion.

Case Report

An 89-year-old woman, previously in good health, woke with sudden acute abdominal pain in her right iliac fossa that spread over the whole abdomen and remained constant until she was admitted 10 hours later. On admission she was in great pain. She denied any previous trauma. The blood pressure was 100/50 mm Hg, haemoglobin 12·3 g, haematocrit 39% and other laboratory findings normal. A straight X-ray of the abdomen showed no definite lesions. A clinical diagnosis of peritonitis was made and laparotomy carried out 2 hours after admission. A retroperitoneal haematoma was found mainly on the right side with extensive bleeding into the mesentery. Both kidneys were palpated but appeared normal, the right being thought to be slightly larger than the left. It was considered that as bleeding had already stopped there was little to be gained from exploration of the retroperitoneal space. Postoperatively there was no evidence of continued bleeding and no blood in the urine at operation or later. She died 9 days later of combined cardio-respiratory failure.

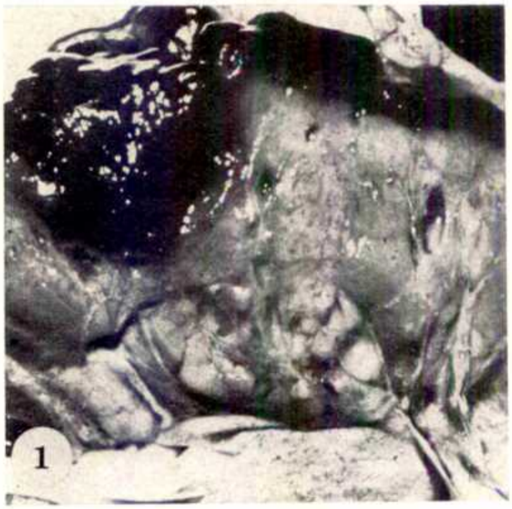
At autopsy (0·92/73) the operative findings were confirmed and supplemented. The *heart* was enlarged (400 g) with left ventricular hypertrophy, and dilated, particularly on the right side. The aorta and renal arteries showed extensive atheromatosis but the lumen of the latter was not reduced. The *kidneys* were of normal size, the renal pelvis and ureters unremarkable. Both kidneys showed arteriosclerotic changes, with a finely granulated surface. The right kidney was surrounded by a subcapsular haematoma up to 1 cm thick that extended into the supra-renal fat. There was a 4 cm in diameter defect in the lower pole of the kidney that was partially filled with organised thrombus (Fig. 1). No definite bleeding point could be defined within or beside this mass, although tortuous grossly arteriosclerotic intralobular arteries were present. Over this area there was a defect in the kidney capsule and the haematoma continued retroperitoneally tracking into the mesentery of the large and small bowel. Here the overlying peritoneum was covered with fibrin. The lungs were oedematous and the parenchymatous organs showed passive venous congestion.

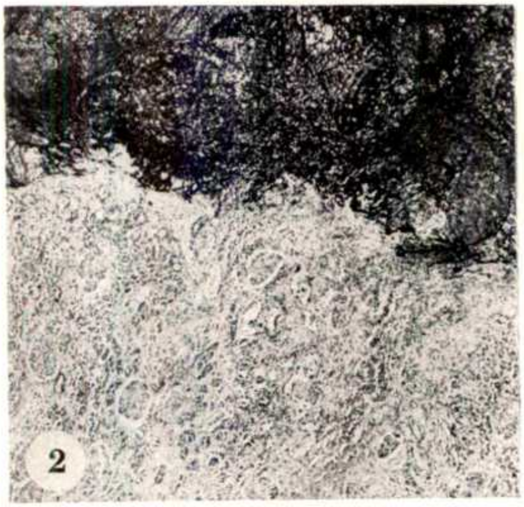
Extensive retroperitoneal bleeding following atraumatic kidney rupture with subsequent reactive changes in the peritoneum, and circulatory failure was considered the cause of death.

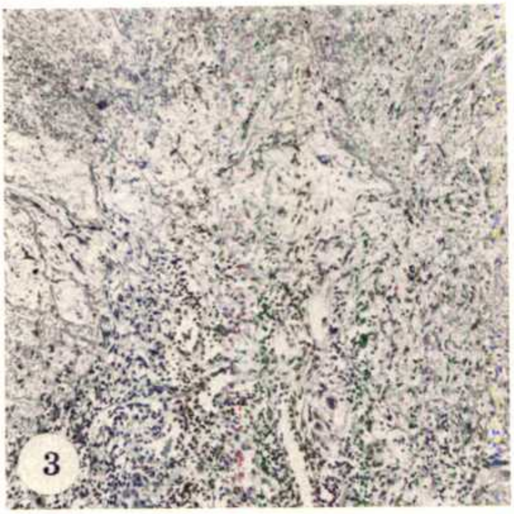
Histology confirmed that the haematoma was sharply demarcated from the renal parenchyma by healthy granulation tissue (Figs. 2 and 3). The parenchyma was well preserved. Some of the glomeruli were sclerotic and the interlobular arteries were arteriosclerotic (Fig. 4). There was no evidence of tumour or of a cyst wall or other renal pathology.

Comment

As in this case atraumatic kidney rupture usually presents with sudden abdominal or flank pain accompanied by signs of shock. Haematuria is frequently present (Polkey and Vynalek 1933; Joachim and Becker, 1965; Howalt and Squires, 1971), but was not seen in this case and her anaemia was not striking enough to suggest bleeding. The investigation of choice diagnostically is renal angiography, as in traumatic cases (Elkin, Meng and deParedes, 1966; Halpern,







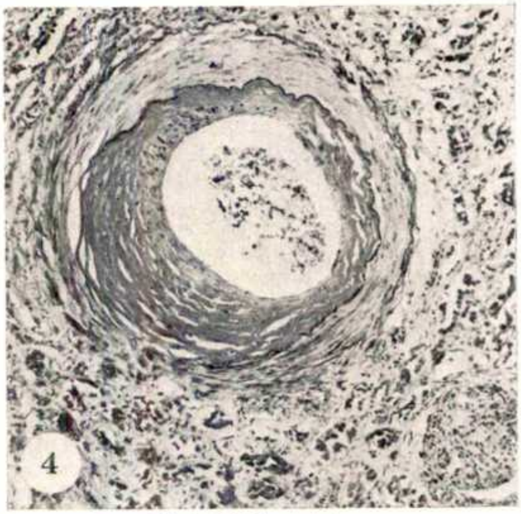


Fig. 1. The cut surface of the right kidney showing defect in parenchyma filled with blood clot.

Fig. 2. The sharp borderline between kidney parenchyma and blood clot. Mallory's PTAH. × 35.

Fig. 3. As Fig. 2—showing granulation tissue. H & E. × 60.

Fig. 4. Arteriosclerotic artery in renal cortex. H & E. × 70.

1968). In the present case the diagnosis was made at autopsy. The histological picture with organised blood clot adjacent to healthy renal tissue suggested that the rupture was due to the bleeding rather than *vice versa*. An arteriosclerotic lesion is most likely although it was not possible to demonstrate the actual vessel with certainty. Atraumatic kidney rupture is rare at present but may be more frequent in transplanted kidneys (Wilson, 1971; Ghose *et al.*, 1973), The surgeon is faced with a retroperitoneal haematoma. If the kidney can be defined as the site of bleeding nephrectomy is usually carried out (Polkey and Vynalek, 1933; Joachim and Becker, 1965). However, Howalt and Squires (1971) consider that conservative treatment is indicated as the basic pathology is bilateral, *i.e.*, hypertensive vascular disease involving the smaller vessels

Table

Cases from the literature of so-called spontaneous rupture of the renal parenchyma, giving author, year, histology, age and blood pressure

Case No.	Author(s)	Histology	Age (yrs)	Blood pressure (mm Hg)
1	Irwin (1943). *U.S. Naval Med. Bull.*, **41**, 818-820	angiomata and pyelonephritis	25	165/105
2	Levy and Hudson (1951). *Brit. J. Urol.*, **23**, 168-170	haemangioma? cyst?	44	180/100
3	Murphy and Harney (1951). *Ann. Surg.*, **134**, 127-130	laceration*	24	normotensive
4	Uson *et al.* (1959) *J. Urol.*, **81**, 388-394	negative	50	"hypertension" (case 6)
5	Valtonen (1966). *Brit. J. Urol.*, **38**, 484-487	negative	59	170/100
6	Howalt and Squires (1971). *Am. J. Surg.*, **123**, 484-488	ischaemic necrosis	58	180/110 (case 1)
7	Howalt and Squires (1971). *Am. J. Surg.*, **123**, 484-488	occlusive vascular disease	75	250/100 (case 2)

* Patient denied trauma.

of the kidney. The extent of the bleeding in the present case suggested rupture of a larger vessel, but even so the bleeding had stopped at the time of operation and did not recur. Thus minimal surgery to control the bleeding may be adequate in the absence of gross renal disease, or advisable in bilateral disease, nephrectomy being reserved for bleeding from obvious renal lesions such as tumours that would justify the operation even in the absence of haemorrhage.

Survey of the literature (see Table) supports Howalt and Squires' (1971) view that hypertensive vascular disease is the underlying lesion, and indicates that the complication occurs primarily in middle age. The designation "renal apoplexy" is perhaps not out of place.

Summary

A case of atraumatic rupture of the parenchyma of the right kidney with gross retroperitoneal haemorrhage is reported in an old woman.

The underlying vascular lesion was probably arteriosclerotic and associated with hypertension.

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Bilateral Pelvi-Ureteric Avulsion Following Closed Trauma

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Bilateral ureteric avulsion at the pelvi-ureteric junction following closed trauma is rare. Providing the diagnosis is made early, successful repair can be achieved. The aetiology remains obscure.

Case Report

A nine-year-old girl was admitted from a peripheral hospital having been involved in a road traffic accident the previous evening. (Details of the accident are unknown.) At that hospital it was noticed that in the 12 hours after admission the child had not passed urine despite adequate hydration. Catheterisation of the bladder revealed only a few ml of blood-stained urine. An intravenous pyelogram was performed (see Fig. 1). Both kidneys appeared normal but there was leakage of contrast from the pelvi-ureteric junctions, appearing in the retroperitoneal space inferior to the kidneys. The ureters and bladder did not fill. There was disruption of the pelvic ring at the left inferior and superior pubic rami but no bony abnormalities were noted of the rib cage or lumbar spine. Skull X-ray showed no fracture. The referring surgeon suggested the possibility of bilateral pelvi-ureteric disruption and transferred the patient to us.

On admission to our unit the child was unconscious, responding only to painful stimuli. She was not shocked, her blood pressure was 150/100 mm Hg. Chest examination revealed adequate, equal air entry to both sides. The abdomen was distended and generalised tenderness and guarding were present. Bowel sounds were absent. Multiple abrasions were noted on the left side of the neck, left shoulder, left lower abdomen and buttock.

Haemoglobin was 14·3 g%, blood urea 102 mg%, electrolytes were within normal limits.

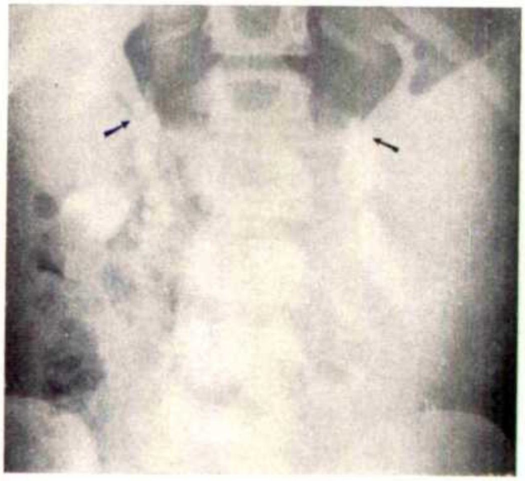
On the basis of the physical examination, laparotomy was performed on the evening of admission to exclude visceral injury. A massive retroperitoneal extravasation of blood and urine was discovered on both sides extending from bony pelvis to the kidney. There was about half a litre of blood-stained fluid in the peritoneal cavity but no viscus was found to be ruptured. The exploration had to be terminated abruptly due to unexplained hypotension. In the postoperative period the cardiovascular status stabilised and the hypertension which had been noted before operation, again became apparent, averaging 140/100 mm Hg. 24 hours after the first laparotomy a further exploration was performed using an upper transverse trans-peritoneal approach. It was noted that both ureters were avulsed about 4 mm below the pelvi-ureteric junction and despite the massive retroperitoneal haematoma no serious trauma had fallen upon the kidneys themselves. Only the left ureter was identified lying about 5 cm inferior to the pelvi-ureteric junction. During the procedure the cardiovascular status again became precarious and prevented further exploration. Bilateral nephrostomies were performed and the patient's abdomen closed. In the postoperative period the patient again developed hypertension averaging 140/100 mm Hg.

The patient's blood pressure returned to normal limits over the next 10 days and her level of consciousness improved so that she could answer simple questions. The bilateral nephrostomies were functioning satisfactorily and the blood urea had returned to normal after 14 days.

2 weeks after the accident a further exploration of the left side was performed and successful anastomosis with some tension was achieved over a FG 3 polythene splint. The nephrostomy tube was left *in situ*. Again in the postoperative period the patient developed hypertension which on this occasion required treatment with an antihypertensive agent.

1 week later, (3 weeks from the time of injury), the right side was explored and the avulsed ureter was found about 2 cm from the pelvi-ureteric junction and anastomosed over a FG 4 polythene splint. The nephrostomy tube was left *in situ*. Again the patient became hypertensive in the postoperative period for 3 days. Urine catecholamines were at no time outside normal limits (No facilities were available for plasma renin estimations.)

Further explorations on both left and right sides were required at 2 months and 8 months respectively for continuing leak from the anastomoses. Secondary repair was performed over a FG 4 polythene splint which was left *in situ* for 5 weeks.



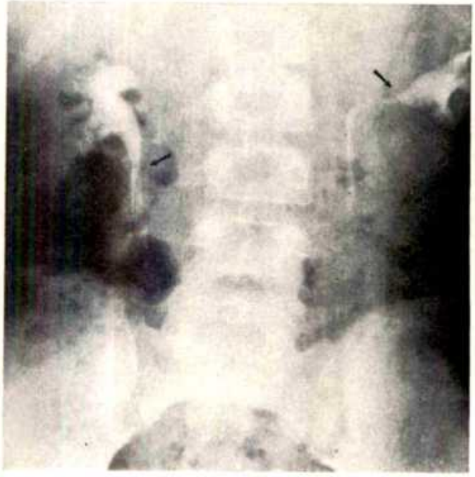


Fig. 1. Intravenous pyelogram about 12 hours after injury, showing leakage of contrast medium from the pelvi-ureteric junction on both sides.

Fig. 2. Intravenous pyelogram one year after injury, showing good drainage on both sides, although the sites of anastomosis are clearly seen.

One year after the injury the girl's general health is excellent. Her blood pressure is 100/70 mmHg and renal function is normal. An intravenous pyelogram shows no sign of hydronephrosis or delayed excretion although the site of anastomosis is clearly seen on both sides. Both kidneys are rotated on their long axis and displaced laterally (see Fig. 2).

Discussion

Bilateral utereric avulsion following closed trauma is rare. Previously, only 3 cases have been reported in the English literature, (2 in adults and 1 in a child) (Ainsworth, Weems and Merrel, 1966; Del Villar, Ireland and Cass, 1972; Johnson *et al.*, 1972). In common with unilateral cases, avulsion occurs just below the pelvi-ureteric junction in the majority of cases. These patients suffer severe multiple injuries and because of this the diagnosis is frequently masked and delayed. Urine collects with blood in the retroperitoneal space making initial exploration difficult but usually primary anastomosis has been achieved over a polythene splint. Delay in diagnosis results in para-renal pseudocyst formation with deterioration in renal function. Recovery of normal anatomy is further prejudiced by retraction of the distal ureter (Bartley *et al.*, 1966; Blancato, 1957; Crosby, 1959; Seright, 1959; Smith, Nanson and Campbell, 1960). Nephrectomy is frequently necessary in such cases.

Haematuria is usually, but not always, present and is frequently apparent on only 1 or 2 occasions. In bilateral cases anuria will result and catheterisation usually produces a small quantity of blood-stained urine. The diagnosis is then difficult to make between rupture of the bladder and that of bilateral avulsion of the ureters. Intravenous and retrograde pyelography are diagnostic. Leaving the retrograde catheter *in situ* aids identification of the ureter at operation.

Extreme lateral flexion and hyperextension of the lumbar spine have been submitted as possible causes of ureteric avulsion. One would expect associated soft tissue and bony injury, but this is not invariably present. It has also been suggested that blunt trauma (*e.g.*, a rubber tyred wheel passing across the abdomen), may displace the kidney upwards, whilst the ureter is relatively fixed, thus causing disruption at the pelvi-ureteric junction (Ainsworth *et al.*, 1966; Bartley *et al.*, 1966; Del Villar *et al.*, 1972; Fruchtman and Newman, 1965).

This case adds little to our understanding of the pathogenesis of the lesion. It is probable that more than one factor is responsible.

Summary

A 9-year-old girl suffered severe multiple injuries in a road traffic accident. Following a period of anuria an intravenous pyelogram was performed indicating bilateral pelvi-ureteric rupture. Continuity was eventually achieved on both sides following two attempts at ureteral anastomosis. One year after the accident the child is well and the kidneys and ureters are functionally normal.

Early diagnosis and treatment is essential in order to achieve a good functional result. This is aided by an awareness of the condition and is confirmed by intravenous and retrograde pyelography. The anastomosis is performed over a polythene splint, supported by a defunctioning nephrostomy for several weeks.

The aetiology remains obscure, although there have been many suggestions regarding the mechanics of pelvi-ureteric avulsion.

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Renal Cell Carcinoma in the Free Wall of a Simple Renal Cyst

A case of a small, well-circumscribed clear cell carcinoma of the free wall of a simple renal cyst is reported.

Case Report

A 49-year-old woman was admitted to the hospital with a doubtful history of haematuria. On admission nothing abnormal was found on physical examination. Urinalysis—*E. Coli.* Blood examination—normal. Intravenous pyelogram and nephrotomogram showed a mass arising from the lower pole of the left kidney which looked like a cyst (Fig. 1). Cystoscopy was normal. The left kidney was explored and 6 × 3 × 2·5 cm cyst containing clear fluid was enucleated. On opening the cyst, a tumour was found in the free wall of the cyst (Fig. 2). Histology proved to be a typical clear cell carcinoma.

Comment

Since the carcinoma was situated in the free wall rather than at the base of the cyst, it is unlikely that the neoplasm, through vascular and tubular obstruction, played a role in the development of the cyst.

The incidence of cyst and tumour co-existing in the same kidney is about 2% to 3%, but tumour arising from the free wall of a simple cyst is rare (Lang, 1971; Passo *et al.*, 1973). In the literature, except for the case reported by Silverman *et al.* (1969) no patient has undergone resection of the cyst alone. We are satisfied with simple enucleation of the cyst in this case because the tumour was in the free wall of the cyst and there was a fibrous rim around the cyst.

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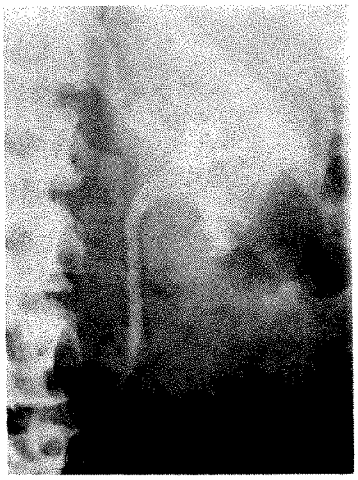

Fig. 1

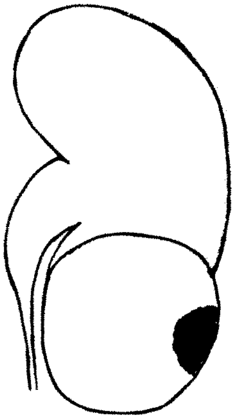

Fig. 2

British Journal of Urology (1975), **47**, 153–159

The Congenital Refluxing Megaureter: Experiences with Surgical Reconstruction

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The association, in children, of vesico-ureteric reflux with urinary infection and pyelonephritic renal scarring is now well recognised and the indications for surgical cure of reflux are, in general, agreed. However, less agreement exists concerning the management of the child with primary refluxing megaureters associated with congenital structural and functional impairment of the kidney parenchyma. The present article is based on our experience with surgical treatment of 18 children with 33 megaureters of this type.

Pathology

The primary refluxing megaureter is unassociated with obstructive uropathy or with neuropathic disease. The ureter shows persistent gross dilatation, as distinct from mere distensibility during the occurrence of reflux, and in addition it is often lengthened and tortuous (Fig. 1 and 2). Fluoroscopy reveals that ureteric peristaltic waves are infrequent and of low amplitude and evacuation is consequently slow, even when the bladder is empty. The kidney shows generalised calyceal dilatation and parenchymal atrophy (Figs. 1, 2 and 3) and considerable functional deficiency is the rule. The bladder, although thin-walled and untrabeculated, is often noted clinically to be persistently distended and at cystography is seen to be of very large capacity (the megaureter-megacystis syndrome). Some authors (de Luca *et al.*, 1962) have been of the opinion that there exists a functional deficiency of the bladder as well as of the ureters, and this concept obtains support from those cases where the urinary stream is poor or when acute retention occurs (Fig. 2). However, micturating cystography shows that the bladder empties completely but that much, or in some instances all, of its content refluxes to the capacious upper tract whence it refills at the end of voiding. The large urinary residue and the occasional occurrence of acute retention are therefore entirely due to reflux and these effects are eliminated when reflux is cured. Similarly, the large bladder capacity would seem to be simply the result of the bladder increasing in size in order to accommodate the large urinary volume which is consequent upon reflux and upon polyuria due to renal insufficiency.

The refluxing megaureter is often encountered in early infancy and is undoubtedly of congenital origin. The renal pathology resembles the atrophic changes caused by back pressure from obstructive uropathy rather than the patchy scarring characteristic of infective pyelonephritis (Figs. 1, 2 and 3). Besides showing parenchymal thinning, the kidney may contain areas of dysplasia indicative of damage inflicted during early foetal life. The causal relationship between the kidney changes, the ureteric dilatation and the vesico-ureteric reflux is not known and can be no more than a subject for conjecture, but it appears likely that non-obstructive, sterile reflux existing prenatally could cause dilatation of the developing ureter and impaired development and maturation of the kidney in the same way as can prenatal urinary obstruction.

The refluxing megaureter, unlike the obstructed megaureter, is more commonly bilateral than unilateral; the proportion in the present series was 14 : 4; the unilateral cases include 1 infant in whom the condition involved only the lower hemi-kidney in a duplex system. The disease more often affects the male than the female; our series contains 15 boys and 3 girls. Clinical

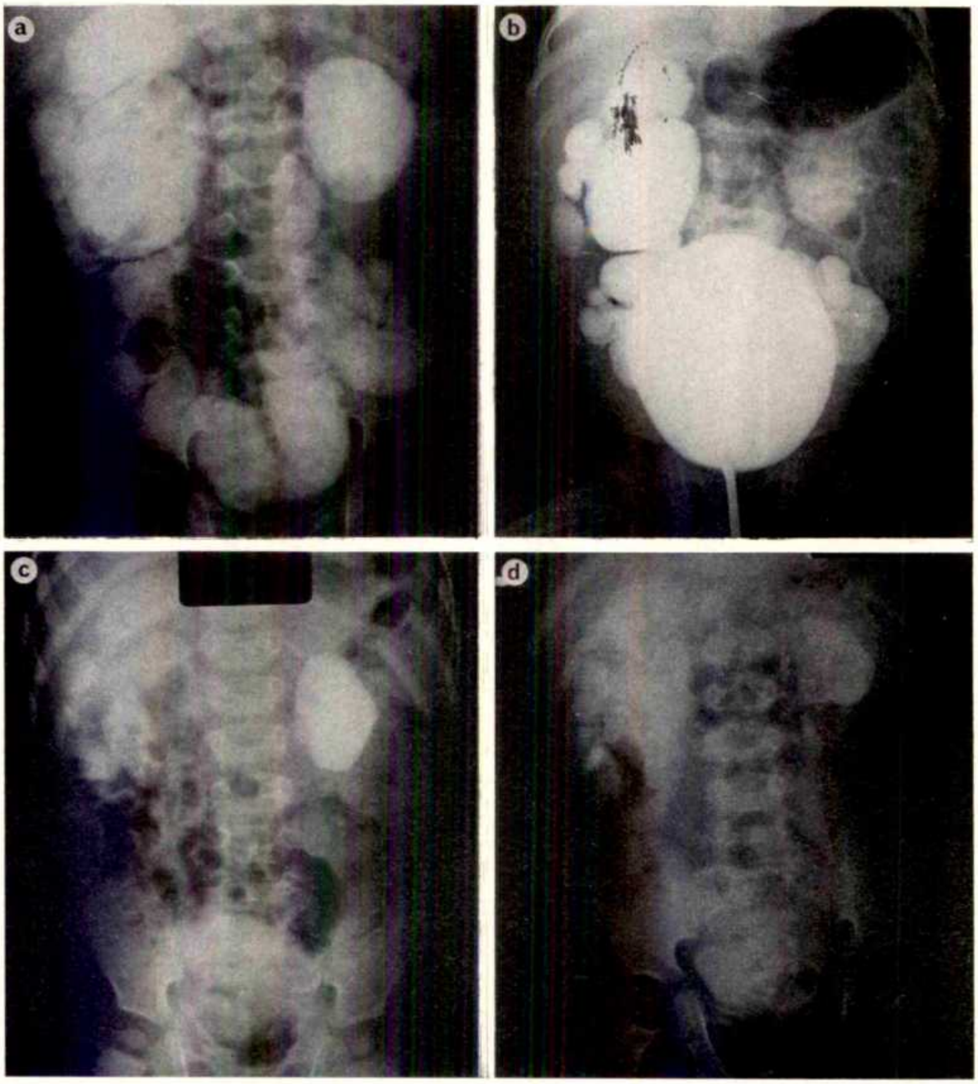

Fig. 1. Bilateral refluxing megaureters in boy. (*a*) I.V.P. aged 7 months. Severe bilateral upper tract dilatation with ureteric tortuosity and angulations at both pelvi-ureteric junctions. (*b*) Cystogram showing smooth-walled bladder and free bilateral reflux. (*c*) I.V.P. after bilateral ureteric tailoring and reimplantation. Residual obstruction at the left pelvi-ureteric junction. (*d*) I.V.P. after left pyelo-ureteroplasty. Both pelves emptying dependently into less dilated and less tortuous ureters. Calyceal dilatation in right kidney not significantly altered.

presentation is in early childhood. All our cases were first seen under the age of 5 years; 3 presented during the first month of life and 5 others were under the age of 6 months. The presenting symptoms were generally referable to azotaemia or infection or both; failure to thrive, vomiting, dehydration, fever and convulsions were common; in some instances urinary retention was a prominent feature.

Surgical Treatment

When a refluxing ureter is undilated, the operative cure of reflux is known to be highly successful but reconstructive surgery for the severely dilated refluxing megaureter has, in the past, generally

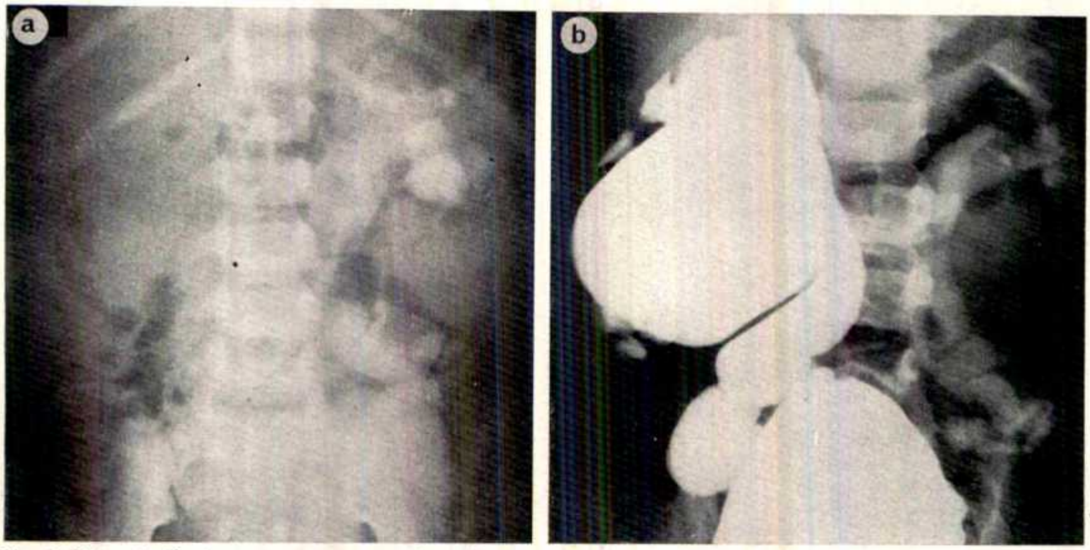

Fig. 2. Bilateral refluxing megaureters presenting with acute retention of urine in a 4 year-old boy. (*a*) I.V.P. showing no concentration by the right kidney. On the left there is severe calyceal dilatation and dilatation and tortuosity of the ureter. (*b*) Cystogram showing bilateral reflux. Voiding was taking place almost entirely up the ureters. The right kidney was shown by pyelostomy to be afunctional.

been considered to be contra-indicated (Williams and Eckstein, 1965; Johnston, 1968). Recently, however, Hendren's (1970, 1972) writings on megaureters have stimulated a reappraisal of this attitude. Hendren has shown that the function of a severely dilated ureter can be improved, and kidney emptying enhanced by shortening and narrowing the ureter, if necessary at both extremities, and reimplanting it into the bladder through a submucosal tunnel to prevent subsequent reflux. Operative narrowing of the ureter aims to restore effective peristalsis by allowing the contraction waves to obliterate the lumen.

Hendren has regarded and treated the chronically dilated ureter as a disease entity, applying the same operative principles to all cases regardless of the underlying causative pathology. Our own experience indicates that a more discriminatory and selective approach is preferable since we have found that the various types of chronic ureteric dilatation show significant differences in their natural history and in their response to therapy. The obstructed megaureter generally responds well to surgical reconstruction as shown by improvement in both ureteric and pelvicalyceal dilatation, but it is necessary with this lesion to narrow only that portion of the ureter which is to be reimplanted into the bladder (Johnston, 1967); the severe hydroureters resulting from obstructive urethral valves frequently show marked spontaneous improvement, both as regards dilatation and tortuosity, after simple destruction of the valves (Johnston and Kulatilake, 1971); the irregularly dilated and tortuous ureters associated with the prune-belly syndrome often empty adequately and show no deterioration with time so that no surgical intervention is needed. Hendren's concept appeared to us to have most application to the congenital refluxing megaureter where, besides the existence of reflux with its consequences of residual urine and possible ascending infection, there is poor drainage of the upper urinary tract because of impaired ureteric emptying.

In the present series nephroureterectomy for a functionless kidney was carried out as a primary procedure in 3 cases and 1 child had a heminephreterectomy. Surgical tailoring of the ureter and reimplantation to the bladder by the standard anti-reflux technique was performed with 29 ureters in 17 patients. With 3 megaureters in 2 patients resection of the upper ureter and the pelvis with pyelo-ureteroplasty was subsequently performed in addition (Figs. 1 and 3). Postoperative cystography showed that reflux had been cured in 16 ureters but persisted in 10. Three

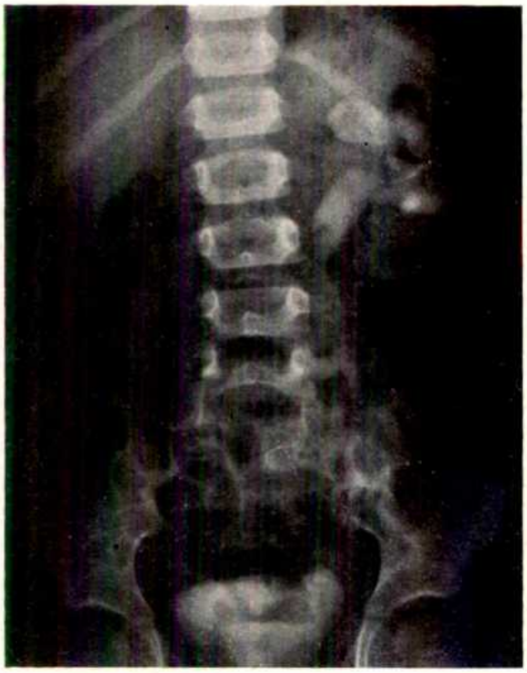

Fig. 2c. I.V.P. after right nephroureterectomy and left ureteric tailoring and reimplantation. Ureter straight and less dilated. Residual calyceal dilatation. Bladder empties normally.

ureters in 2 patients developed an obstruction at the uretero-vesical reimplantation which was demonstrated by increased upper tract dilatation on postoperative intravenous urography. These 3 ureters and 6 of those with persistent reflux were reimplanted for a second time; the obstruction was relieved in each case and 7 of the 9 ureters were subsequently free of reflux; in 2 reflux was still present.

Postoperative excretion urography in those cases where the reflux was cured, and there was no ureteric obstruction, showed that ureteric tortuosity had been eliminated in most and that there was a lessening of ureteric dilatation in many, but significant improvement in pelvi-calyceal dilatation was apparent mainly in those cases in which pyelo-ureteroplasty had been performed because of secondary angulation and obstruction at the pelvi-ureteric junction (Fig. 3). This finding, and also the fact that postoperative isotope renography showed persistently rising tracings in each of 8 patients in whom it was performed, suggest that little improvement in kidney emptying had been obtained.

The urine has been persistently free of infection after surgery in 9 patients, of whom 1 still has reflux and 8 have not. In 8 children intermittent urinary infection persisted; 3 of these still have reflux and 5 have not.

One girl in this series died of chronic renal failure at the age of 12 years. A boy of 7 years is severely azotaemic and in 4 other children the blood urea is persistently above 40 mg %. Accurate assessment of renal function by clearance studies is difficult in young children particularly, as in the present series, when incomplete urinary evacuation exists and we do not believe that pre- and postoperative estimations give valid information concerning changes in parenchymal activity. In the growing child observation of the height percentile offers a fair indication of the adequacy of kidney function. 8 children in the present series with bilateral disease, including the child who died, are, or were, seriously stunted in growth, being on or below the 3rd height percentile; 2 are at the 50th percentile or over and 3 are over the 97th. No patient has shown a rise in height percentile after surgery and 2 have had a decrease.

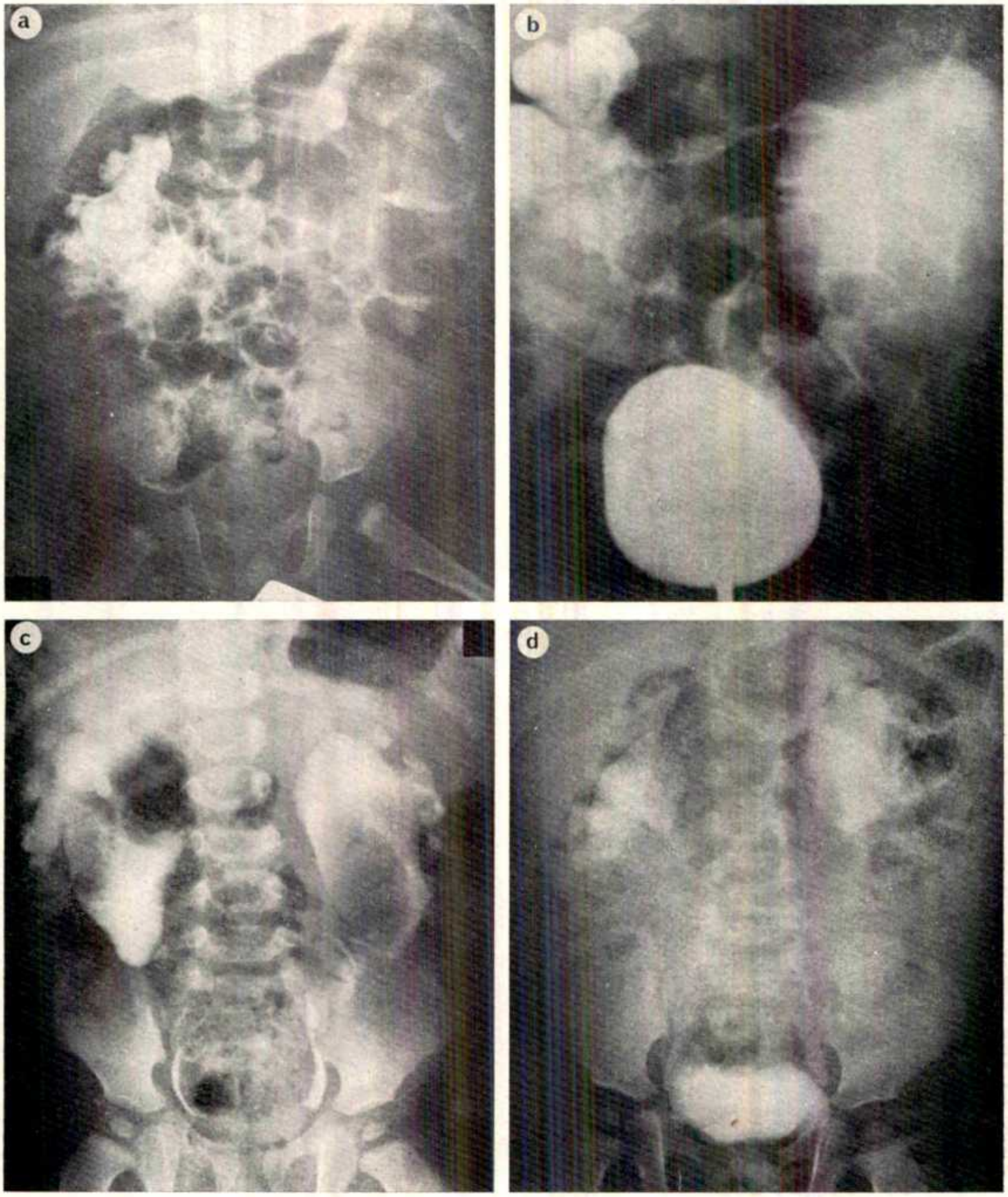

Fig. 3. Boy with bilateral refluxing megaureters with secondary obstruction at each pelvi-ureteric junction. (*a*) I.V.P. aged 6 months. Right pelvi-calyceal dilation. On the left only very dilated calyces are seen. (*b*) Cystogram showing bilateral ureteric dilatation and tortuosity. Severe dilatation of the pelves and pelvi-ureteric angulations. (*c*) I.V.P. after bilateral ureteric tailoring and reimplantation. Improved appearance of ureters but obstructive angulations persist at the pelvi-ureteric junctions. (*d*) I.V.P. following bilateral pyelo-ureteroplasty showing improved pelvic emptying.

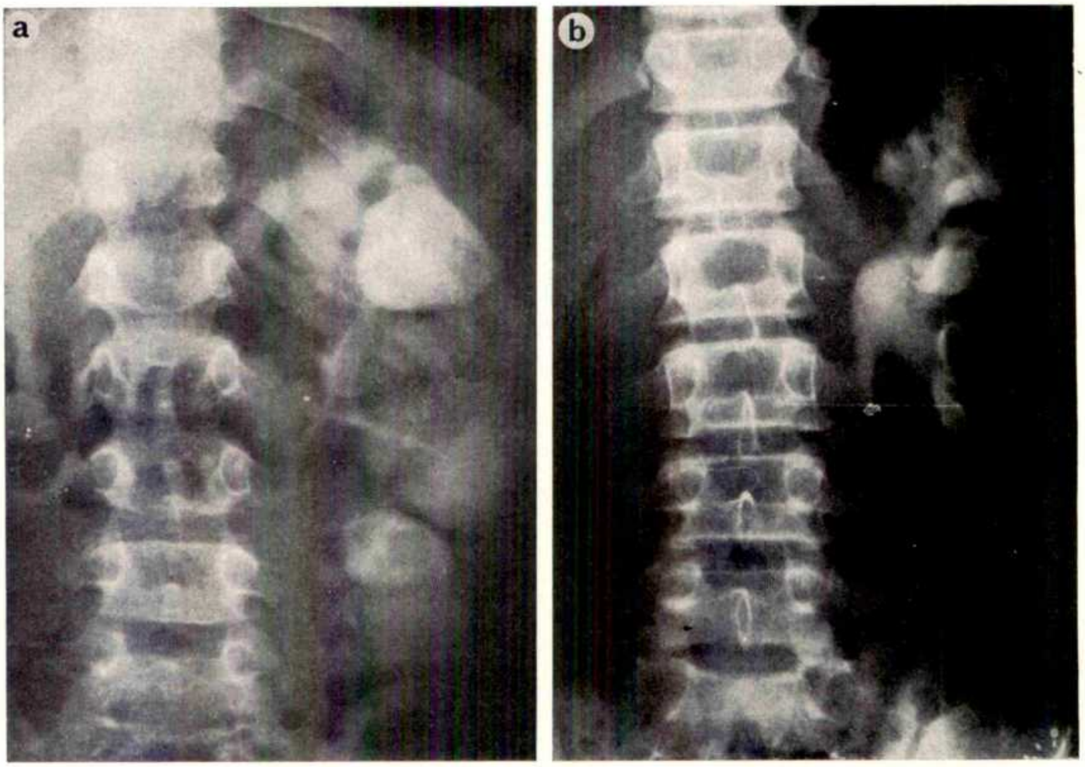

Fig. 4. I.V.P.s of obstructed megaureter affecting solitary left kidney in a 6 years old boy. (*a*) Before surgery. Severe calyceal dilation. (*b*) 5 years following ureteric reimplantation and pyelo-ureteroplasty for secondary obstruction at the pelvi-ureteric junction. Marked improvement in calyceal dilatation.

Discussion

We are loath to believe that the unsatisfactory results of surgery in this series can be attributed entirely to inadequacies in our operative technique and we prefer to think that a most important factor was the poor quality of the materials we have had to deal with. In our experience the surgical cure of primary reflux with undilated ureters approaches 100%. With megaureters the situation differs in that the thickening of the ureteric wall makes the narrowed, reimplanted lower extremity of the ureter relatively rigid and incompressible so that even when the intravesical segment is of adequate length, the flap-valve action of the normal uretero-vesical junction is lacking. Ureteric obstruction following reimplantation, which occurred with 3 ureters in our series, was not due to fibrous stricturing; at re-operation there was some angulation of the extravesical ureter at its entry to the bladder but our impression was that the narrowed, but patent, lower ureter was a site of relative obstruction simply because of the inadequacy of the ureteric peristalsis above. Lack of obvious postoperative improvement in pelvi-calyceal emptying can similarly be attributed to a lack of improvement in ureteric propulsion of urine. In this respect our results with the refluxing megaureter are in marked contrast with those obtained with the obstructed megaureter where peristalsis is generally vigorous, or at least recoverable, and in which obvious, and sometimes striking radiological improvement is to be expected after surgery (Fig. 4).

Our experiences with this series lead us to conclude that the existence of bilateral refluxing megaureters in a child is not, of itself, an indication for surgery. We would now advise that operative tailoring and reimplantation of these severely inadequate and slowly-emptying ureters should be undertaken mainly in those cases in which an obstructive element occurs as a result of the reflux. That is, when there is a very large vesical residue consequent upon voided urine following the path of least resistance into the upper urinary tract rather than down the urethra, or when reflux is causing angulation and obstruction at the pelvi-ureteric junction; this pelvic obstruction may, in some instances, be relieved by curing the reflux (Fig. 1) but in others the angulation has become fixed and pyelo-ureteroplasty is required in addition (Fig. 3). Otherwise, we would prefer non-operative management unless there is evidence or suspicion that further damage to the congenitally impaired kidney parenchyma is occurring as a result of ascending infection which cannot be controlled by chemotherapy. In conservative management, the performance of triple micturition (Stephens, 1957) is helpful in the elimination of urinary residue and the control of infection but the method is obviously only useful in the child who is old enough to understand what is required. External urinary diversion by cutaneous ureterostomy or intestinal conduit has, we believe, only a very limited application to children with this disorder. The child who had urinary control, is burdened with the physical, and on occasion the emotional, disabilities consequent upon a urinary stoma, but he obtains little benefit in exchange. In our experience of similar severely and irreversibly dilated upper tracts resulting from bladder neuropathy, diversion seldom leads to any obvious improvement in kidney function and the onset of overt renal failure is not significantly delayed. We would restrict diversion with refluxing megaureters to the case in which reconstructive surgery, employed according to the indications given, has failed and ascending infection continues to endanger renal function.

Summary

A series of 17 children with congenital refluxing megaureters underwent ureteric tailoring and reimplantation.

The results obtained suggest that such surgery should be restricted to those cases in which an obstructive element is introduced as a result of the reflux or in which ascending infection is further damaging the already prenatally defective kidney parenchyma.

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Short Case Report

Ileo-vesical Fistula with Phytobezoar in Crohn's Disease of Ileum

An ileo-vesical fistula with phytobezoar developed 7 years after a simple by-pass operation for an obstructing acute Crohn's disease of the terminal ileum. Fistulae can occur in Crohn's disease, but we have been unable to trace a similar case with bezoar. (Crohn, 1958, De Bakey & Ochsner, 1938) This might have been avoided with an exclusion by-pass or resection of the ileum (Edwards, 1969).

Case Description

A male aged 23 presented in 1965 with 9 months' intermittent abdominal pain and 3 days' symptoms of small bowel obstruction. Emergency laparatomy revealed acute obstructing Crohn's disease of the terminal 18 inches of ileum; an ileo-colic anastomosis without exclusion was done with relief of symptoms.

In 1972, he presented with 3 months' lower abdominal pain, frequency and occasional pneumaturia. A tender mass could be felt bimanually, arising in the pelvis.

Intravenous urography and cystogram were normal except for deformity of the fundus of the bladder. Gastrointestinal series were normal. Cystoscopy revealed chronic cystitis but no fistula was seen.

Laparotomy revealed a phytobezoar measuring 9×5 cm (Fig. 1) in the by-passed ileum. An ileo-vesical fistula had resulted due to suppuration. The gut from "A" to "B" was resected (Fig. 2). Histologically, Crohn's disease was again confirmed. Closure of the bladder defect and appendicectomy led to an uneventful recovery and the patient remains symptom free.

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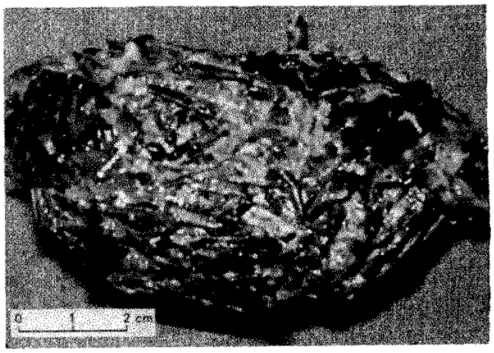

Fig. 1. The phytobezoar.

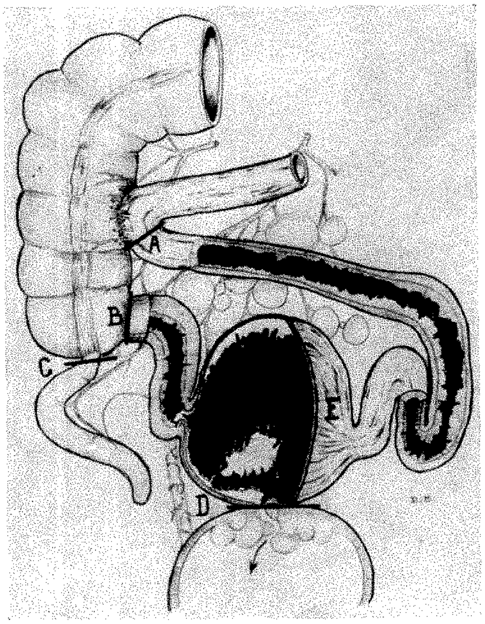

Fig. 2. Showing previous anastomosis and the bypassed segment of ileum (A to B) which was resected at the second operation. Appendix (C), fistula (D) and phytobezoar (E).

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British Journal of Urology (1975), **47**, 161–175

Urodynamic Observations Following Spinal Trauma

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The long-term survival of a patient with a complete spinal cord transection depends mainly on the prevention of urological complications which arise from the altered physiology of the bladder.

The sacral segments of the spinal cord (S.2.3.4) containing the parasympathetic upper motor neurone to the detrusor lie opposite the body of the first lumbar vertebra. Spinal transection above these sacral segments leaving them undamaged and free of higher control will eventually lead to the development of reflex micturition (the reflex or upper motor neurone type of bladder).

With total destruction of the sacral cord segments or their outflow tracts the bladder becomes an inert sac which can only be emptied by a rise of intra-abdominal pressure (the flaccid or lower motor neurone type of bladder).

When classifying the type of bladder according to the level of the spinal cord damage it must be remembered that even with high lesions, *e.g.* D.8, there may be complete infarction of the cord below that level resulting in a flaccid (LMN) bladder.

The urological management of patients following spinal trauma must be based on as much objective evidence of the altered physiology as is possible. Investigations such as bacteriology of the urine, measurement of residual urine, intravenous urography and micturating cysto-urethrography all give objective evidence of the results of the patho-physiology of the urinary tract but do not give an accurate assessment of the urodynamic problems which produce urinary tract complications.

This paper describes the results of urodynamic studies performed on patients with traumatic spinal cord damage over the past 3 years. These studies began as a research procedure but now have become part of the routine investigations of such patients. Over 250 such investigations have now been performed in over 100 patients.

Methods

Two investigations are performed:

1. Measurement of the urethral pressure profile.
2. Pressure-flow studies during bladder filling and voiding with synchronous X-rays.

1. Urethral Pressure Profile (Fig. 1)

This method is similar to that described by Brown and Wickham (1969).

2. Pressure-flow Studies with Synchronous X-rays

Our method of investigation is similar to that described by Bates and Corney (1971) but with considerable modifications for its application in the study of paraplegic and quadraplegic patients.

The paralysed patient has to lie on the X-ray table in the supine right oblique position.

All filling of the bladder has to be done slowly (4 ml/per min).

Read at the 30th Annual Meeting of the British Association of Urological Surgeons in Torquay, June 1974.

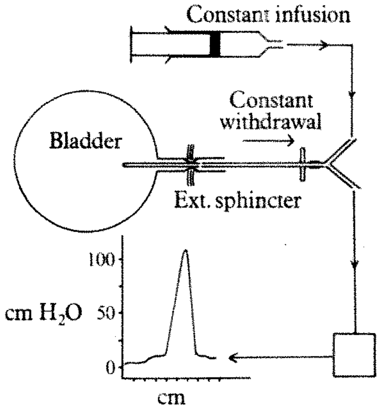


Fig. 1. Diagram of urethral profile measurement.

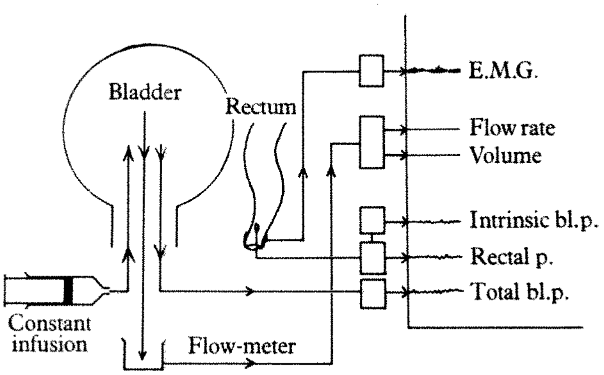


Fig. 2. Diagram of pressure-flow studies.

In patients with reflex micturition but with high residual urines the bladder is never emptied with a catheter prior to performing a pressure-flow study. Both rapid filling or emptying the bladder prior to investigation may completely alter the reflex pattern of the bladder giving a false urodynamic pattern.

Figure 2 shows a diagram of the method.

A bi-lumen nylon catheter (external diameter 1·4 mm) is passed into the bladder transurethrally. One channel is used for filling the bladder with contrast medium (Urografin 35%) delivered from a constant infusion pump at 4 ml per min (Harvard contant infusion pump, model 901).

The second limb of the catheter records the total bladder pressure (Transducer S.E. 4-82).

A fluid-filled rectal catheter protected with a finger cot records the rectal pressure (Transducer S.E. 4-82).

The third channel records the electronically subtracted difference between the total bladder pressure and the rectal pressure, this being the true detrusor or intrinsic bladder pressure.

Voided urine is passed into the beaker suspended from a weighing transducer (Devices Instruments Ltd. type U.F.1) via a length of plastic drainpipe (internal diameter 4·5 cm). From this transducer the voided volume and flow rate (ml per sec) are electronically calculated and recorded on the fourth and fifth channels of the pen recorder (Watanabe 6 channel Multicorder).

The sixth channel records an integrated electromyogram (EMG) of the external anal sphincter using Disa bi-polar EMG needles. The electrical activity thus recorded represents the overall activity of the pelvic floor musculature including the external urethral sphincter. The EMG is also monitored through a loud-speaker. In a patient with a severe reflex spasm of the lower limbs and buttocks it may be extremely difficult to maintain the EMG needle in the correct position.

X-rays were taken using the Elema-Schonander autochanger.

Results

Immediately following severe spinal injury there is depression of all neuronal activity below the level of the lesion. Then after a varying time there is a progressive return of somatic and visceral reflex activity in those intact cord segments below the level of the cord damage.

The following results of urethral pressure profile measurements and pressure-flow studies were all obtained in male patients with spinal cord damage above the sacral cord segments with developing or established reflex micturition. All patients studied had either complete spinal transection or only minimal sensory sparing with complete motor loss.

1. The Urethral Pressure Profile in Patients with Returning Reflex Activity (Figs. 3 to 5)

Serial measurements of the pressure profile were performed over the weeks and months following spinal trauma.

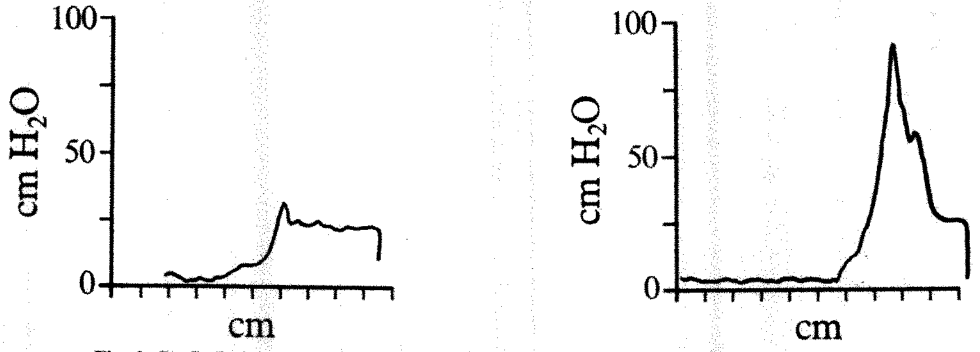


Fig. 3. R. C. D.4 (complete) urethral profile. 3 weeks post-injury and 6 weeks post-injury.

Months post-injury	Pressure (cm H2O) Ext. Sph.
5	60
7	135

Fig. 4. V. D. ♂ 24. D.4 complete.

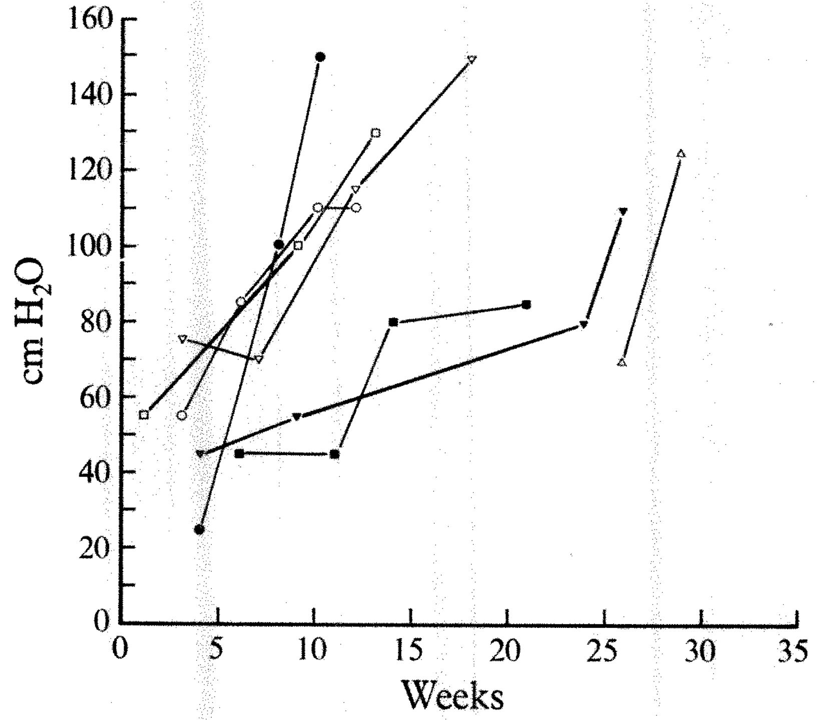


Fig. 5. Urethral pressure/time post-injury.

Figure 3. Male patient, age 17, complete paraplegia D.4. This shows how the pressure at the external urethral sphincter rises from 30 cm H_2O 3 weeks after injury to nearly 100 cm H_2O at 6 weeks.

Figure 4. Male patient, age 24, complete paraplegia D.4 showing a rise of pressure at the external urethral sphincter from 60 cm H_2O 5 months after injury to 135 cm H_2O 2 months later.

Figure 5. This graph illustrates the overall rise of pressure recorded at the external urethral sphincter in 7 patients in the weeks following injury. Each different symbol represents a single recording in the same patient. Eventually the external sphincter pressure often rises to a range well above that found in the normal male. In most patients this external sphincter pressure can be reflexly reinforced by tapping the lower abdominal wall when pressures in excess of 300 cm H_2O are commonly recorded.

All urethral pressure profile measurements are static measurements and may bear no relationship to the external urethral sphincter pressure during micturition.

2. *Pressure-flow Studies in Patients with Returning Detrusor Activity*

The following results (Figs. 6 to 17) illustrate the different urodynamic patterns seen in male patients with developing or established reflex micturition. They all differ widely from the situation in the neurologically normal person when, during micturition, the EMG of the pelvic floor is silent and the bladder empties in one continuous flow and emptying is complete.

Examples of differing urodynamic patterns are shown:

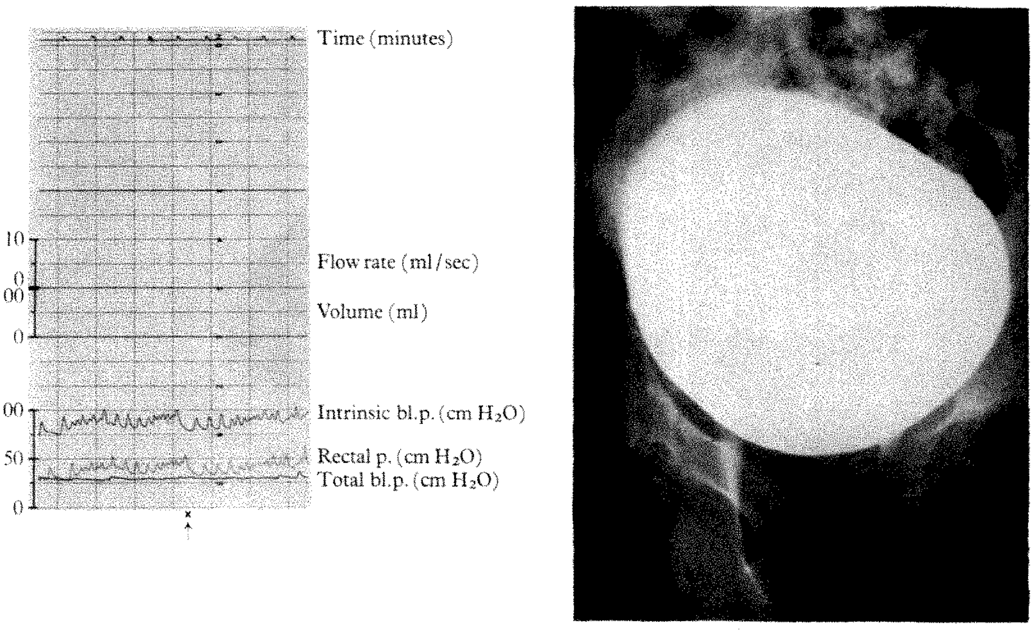


Fig. 6. Male, age 17, complete quadriplegia C.6. 6 months after injury. This shows prolonged reflex detrusor activity (50 cm H_2O) with minimal "opening" of the bladder neck (X). There was no voiding.

(a) *Early Reflex Activity*

The first return of reflex detrusor activity may be insufficient to "open" the bladder neck and produce voiding. Figure 6 illustrates this prolonged reflex detrusor activity (50 cm H_2O) which produced only very poor opening of the bladder neck.

Figure 7 illustrates the commonly seen prolonged reflex detrusor contraction (50 cm H_2O) with delayed opening of the bladder neck. Eventually low flow rate and intermittent voiding takes place (max. flow rate 3 ml/sec). This low flow rate is due to increased outflow resistance from both poor "opening" of the bladder neck and also a degree of detrusor sphincteric imbalance. Bladder emptying was incomplete with high residual urines.

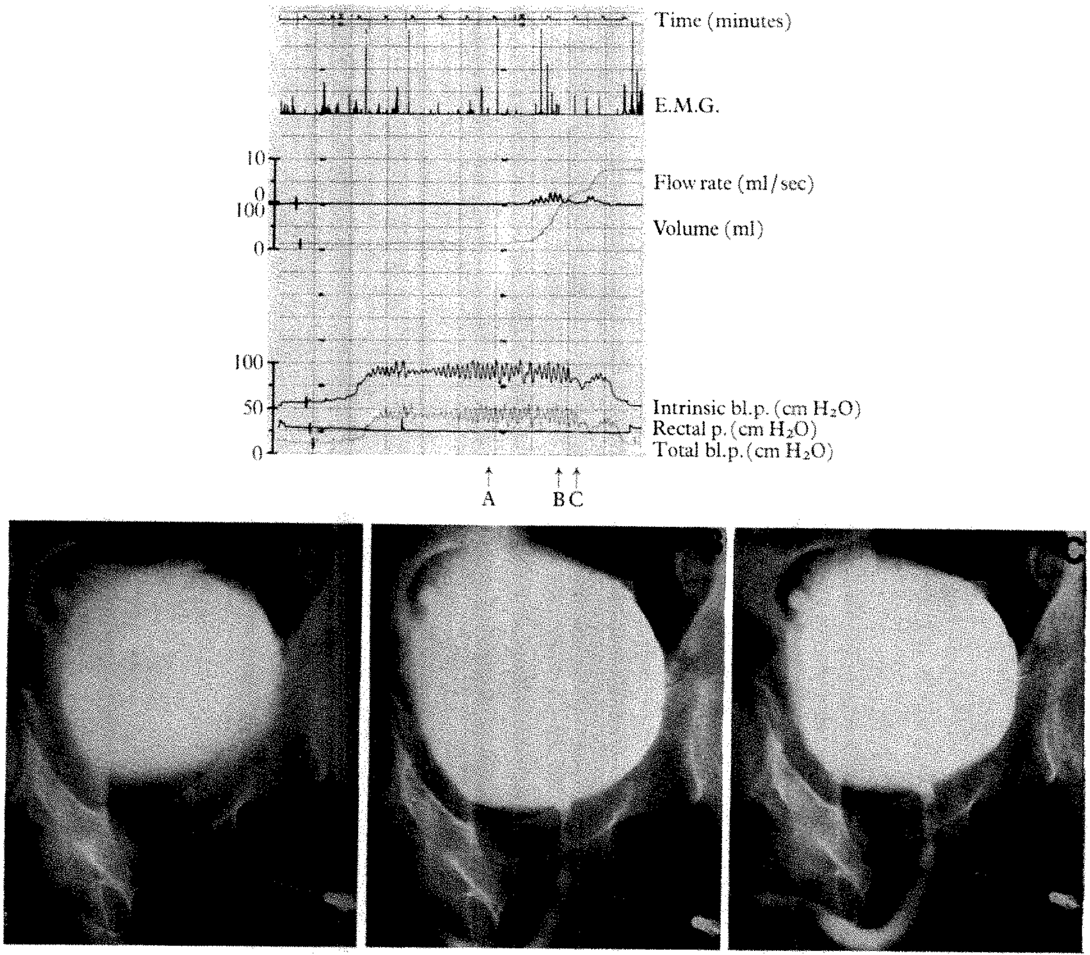


Fig. 7. Male, age 20, quadriplegia C.6 with minimal sensory sparing. 6 months after injury. This shows prolonged reflex detrusor activity (10 min 50 cm H_2O). At first with only very poor "opening" of the bladder neck (A). Maximal voiding rate is 3 ml/sec. X-rays B and C again show incomplete "opening" of the bladder neck. There is incomplete bladder emptying with high residual urines.

Although poor "opening" of the bladder neck is occasionally seen during this early reflex recovery the most common problem is the development of an imbalance between the detrusor and the somatic sphincteric mechanism. The mass reflex action centred on the sacral cord segments produces not only detrusor contractions but also external sphincter contractions which presents a functional obstruction to urine flow. This detrusor sphincteric imbalance is shown by the following features:

(i) Increased EMG activity of the pelvic floor during a reflex detrusor contraction.

(ii) Often considerable delay in the onset of voiding with a complete hold-up of urine at the external sphincter.

(iii) Low flow rates and intermittent voiding.
(iv) Often sudden interruption of the urine stream by spasm of the external sphincter.

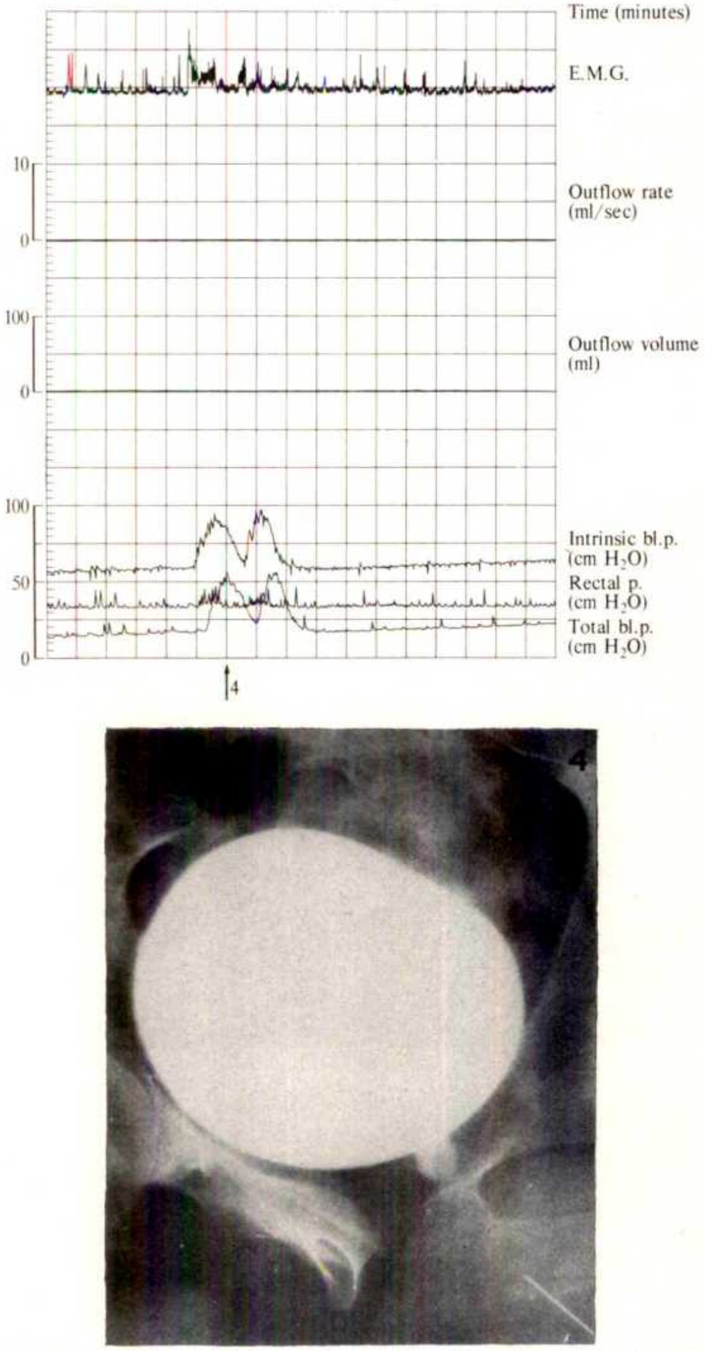


Fig. 8. Male, age 20, complete quadriplegia C.5 15 months after injury. The pressure trace shows a reflex rise in detrusor pressure in response to tapping the lower abdominal wall (45 cm H_2O). This rise in pressure was associated with increased EMG activity. X-ray 4 shows an "open" bladder neck with complete hold-up of contrast at the external urethral exterior. There was no voiding.

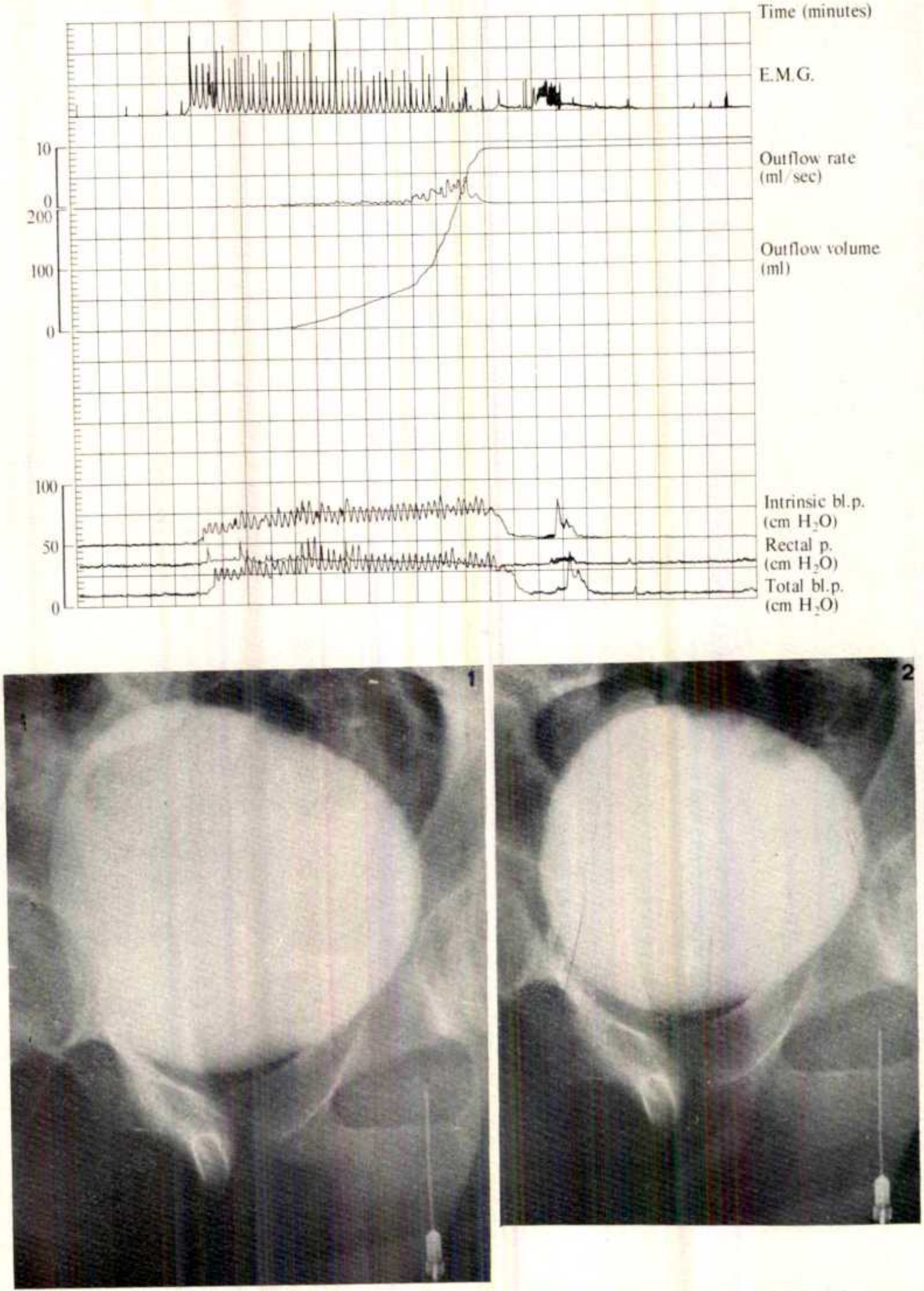


Fig. 9. Male, age 17, complete paraplegia D.4. 6 weeks after injury. This shows prolonged (8 min) reflex detrusor activity (max. 35 cm H_2O) associated with a marked phasic increase of pelvic floor EMG activity. There is delay in the onset of voiding (2·5 min) during which the bladder neck is "open" with complete hold-up at the external sphincter (X-ray 1). Eventual voiding is intermittent and of low flow rate, rising to a maximum of 4·5 ml/sec, when the EMG is at its lowest level. X-ray 2 at this time shows only minimal narrowing at the external sphincter. Bladder emptying was incomplete despite reinforcement with tapping.

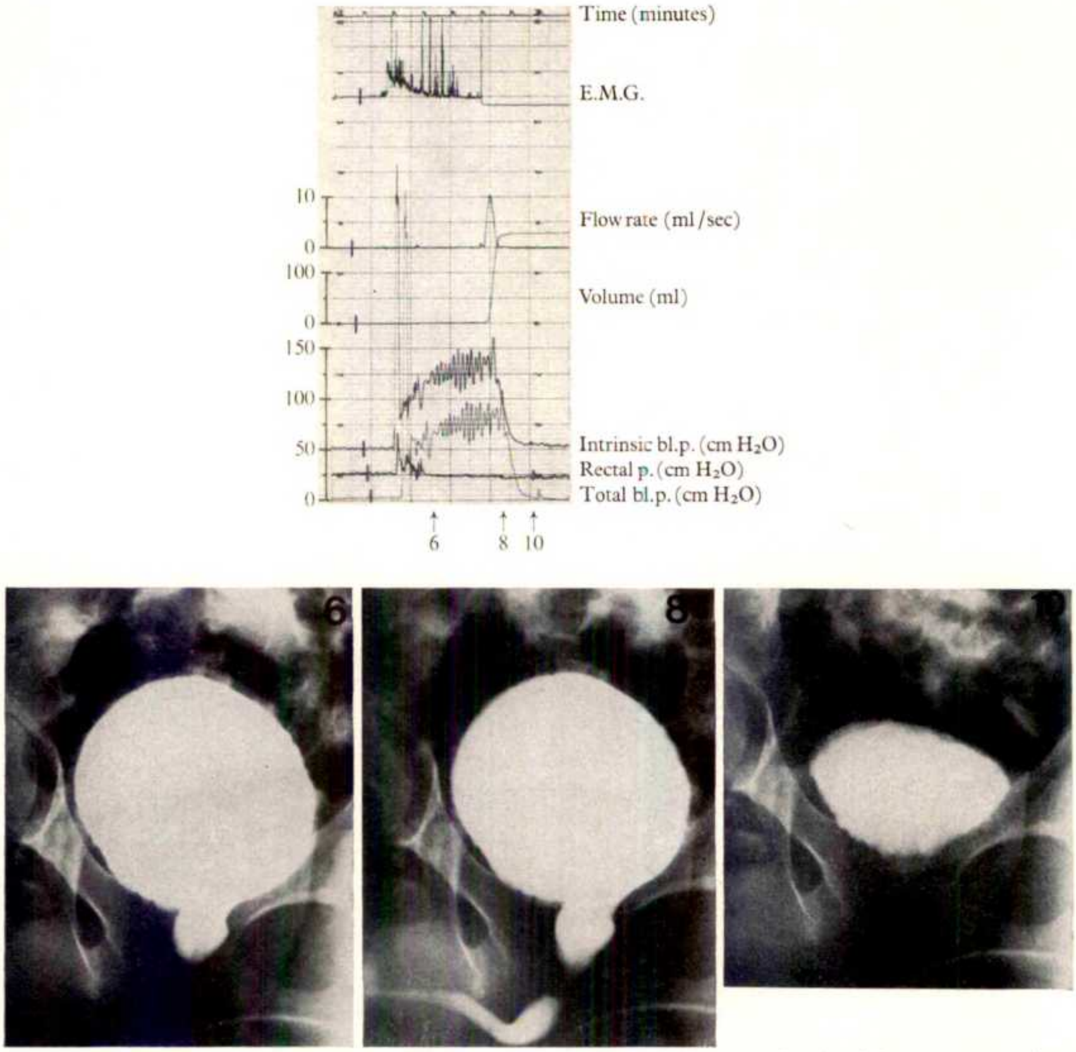
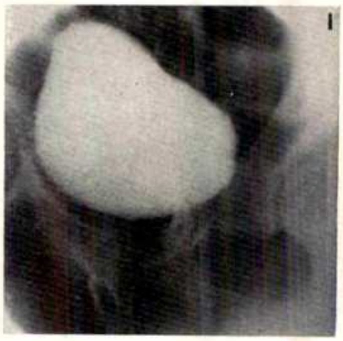


Fig. 10. Male, age 17, complete paraplegia D.6. 15 months after injury. This shows a reflex rise of detrusor pressure (max. 100 cm H_2O) accompanied by a marked increase in the pelvic floor EMG. There is delay in the onset of voiding (3 min) with complete obstruction at the external urethral sphincter (X-ray 6). Maximal voiding 10 ml/sec, even then with considerable functional obstruction at the external sphincter. Incomplete bladder emptying despite re-inforcement. (R.U. = 100 to 150 ml.)

Fig. 11. Male, age 16, complete paraplegia D.5. 4 months after injury. Reflex rise of detrusor pressure (2 min) up to 175 cm H_2O with marked increase of pelvic floor EMG. Initial hold-up at the external sphincter (X-ray 1). Eventual voiding (1 ml/sec) with functional obstruction at the external sphincter. Maximal flow rate 3 ml/sec achieved when the external sphincter relaxes as shown by the diminished EMG activity and X-ray 3. Incomplete bladder emptying (with reinforcement) with high residual urines. (See right.)

Fig. 12. Male, age 36, complete paraplegia D.11. 3 months after injury. Reflex rise of detrusor pressure (3·5 min 60 cm H_2O) associated with increased pelvic floor EMG. Delay in onset of voiding with obstruction at the external sphincter (X-ray 3). Max. flow rate 5 ml/sec (X-ray 6). Sudden cessation of urine flow with spasm of the external sphincter (X-ray 8) associated with an increase in the EMG and a rise of detrusor pressure to 85 cm H_2O. Low residual urines (less than 80 ml) obtained with reinforcement by tapping. (See right.)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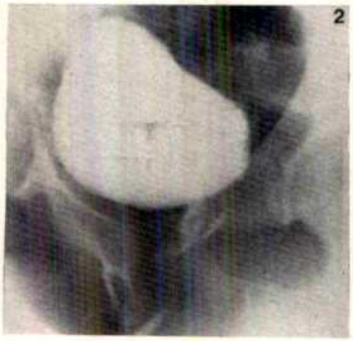
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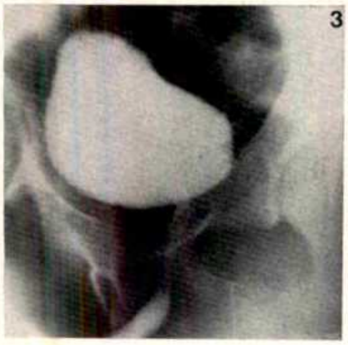
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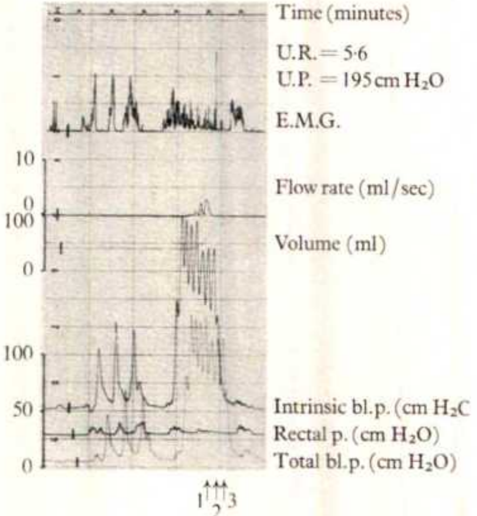
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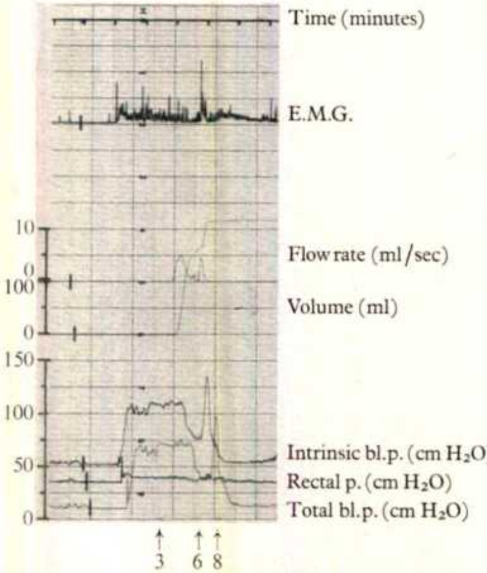
U.R. = 5·6
U.P. = 195 cm H₂O
E.M.G.
10
Flow rate (ml/sec)
0
100
Volume (ml)
0
100
50
Intrinsic bl.p. (cm H₂C
Rectal p. (cm H₂O)
0
Total bl.p. (cm H₂O)
1
2
3


Time (minutes)
E.M.G.
10
Flow rate (ml/sec)
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Volume (ml)
0
150
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Rectal p. (cm H₂O)
0
Total bl.p. (cm H₂O)
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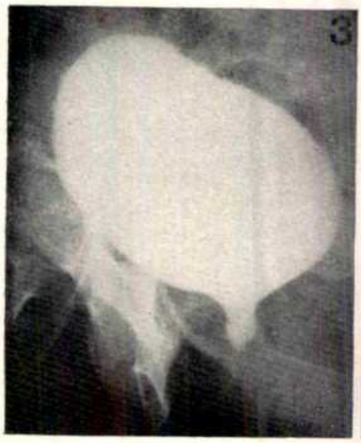
6
8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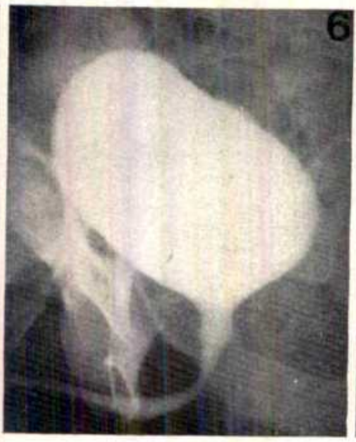
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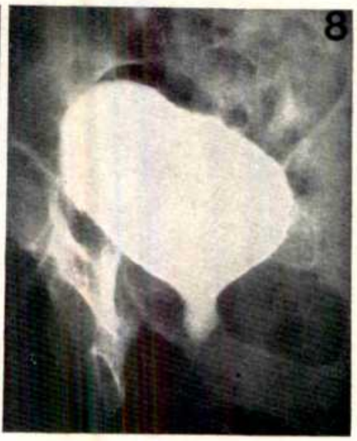
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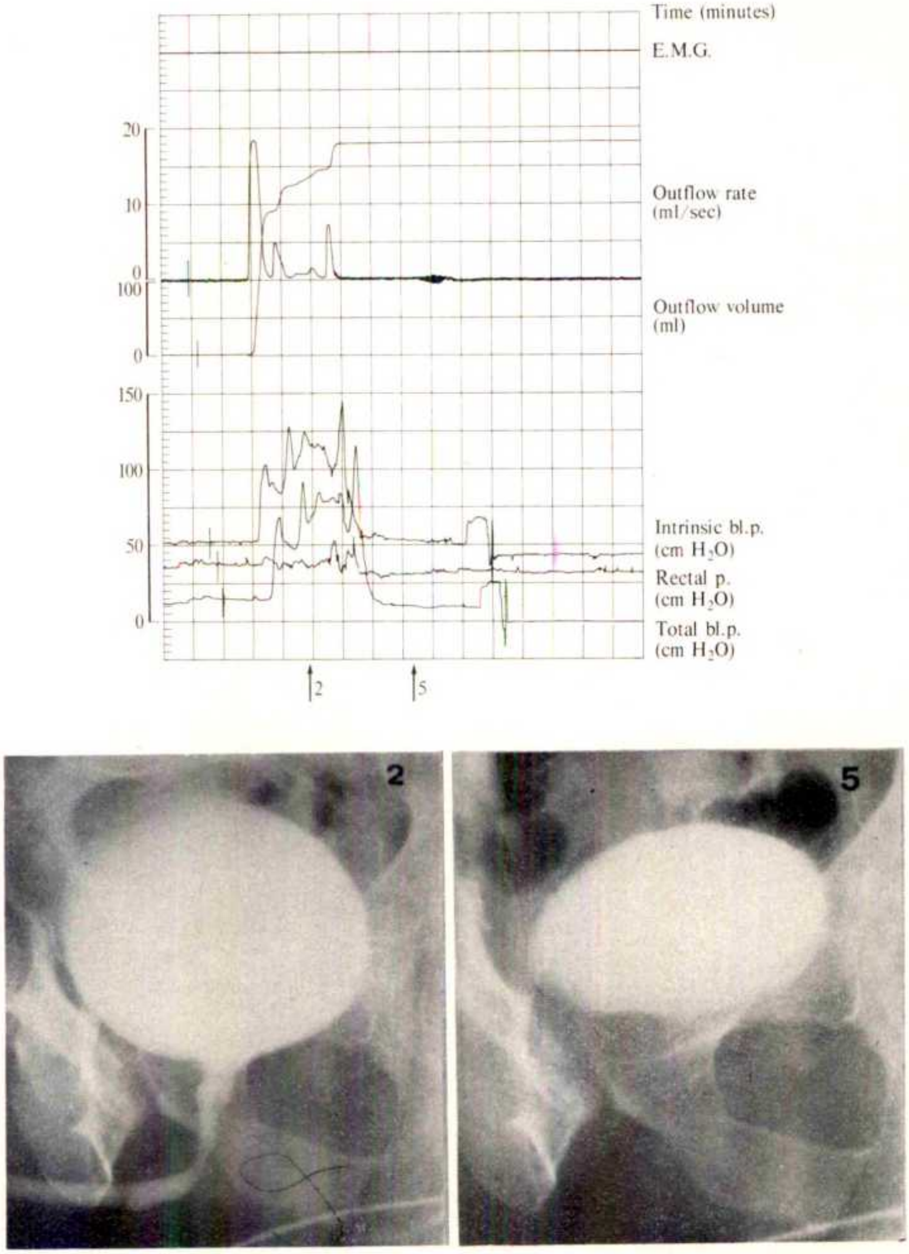
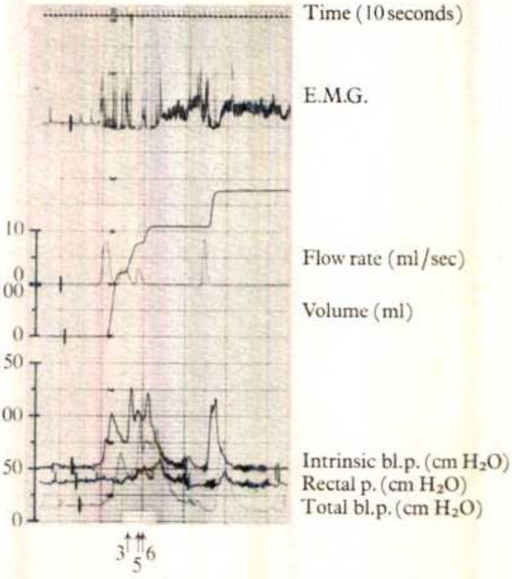


Fig. 13. Male, age 36 (same patient as in Fig. 12). 6 months after injury. (No EMG). Reflex rise in detrusor pressure (55 cm H_2O) producing immediate voiding (18 ml/sec) (X-ray 2). Interruption of stream with maximum pressure rise (90 cm H_2O) due to external sphincter spasm. Residual urines less than 80 ml (with tapping).

Fig. 14. Male, age 36 (same patient as in Figs 12 and 13). 18 months after injury. Reflex rise of detrusor pressure, at first to 55 cm H_2O, with immediate voiding (8 ml/sec) (X-ray 3). Marked increase in pelvic floor EMG. Interruption of voiding stream by spasm at the external sphincter (X-ray 5) with rise of detrusor pressure to 80 cm H_2O. Relaxation of the external sphincter produced further voiding (3 ml/sec) (X-ray 6). Residual urines low (with tapping). (See right.)


Time (10 seconds)
E.M.G.
10
0
Flow rate (ml/sec)
100
Volume (ml)
0
150
100
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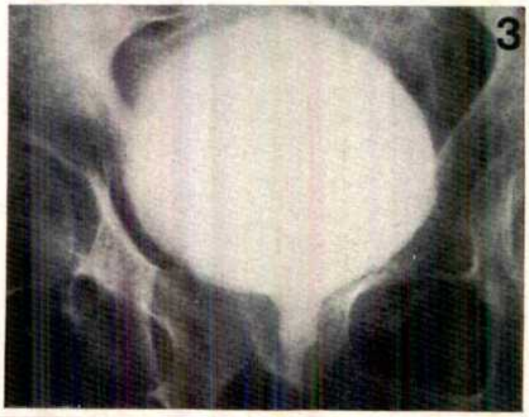
Intrinsic bl.p. (cm H_2O)
Rectal p. (cm H_2O)
Total bl.p. (cm H_2O)
3
5
6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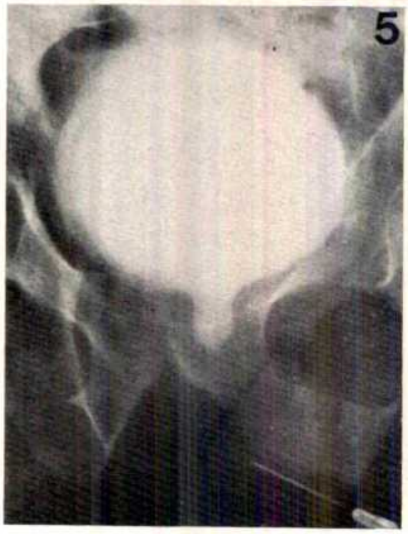
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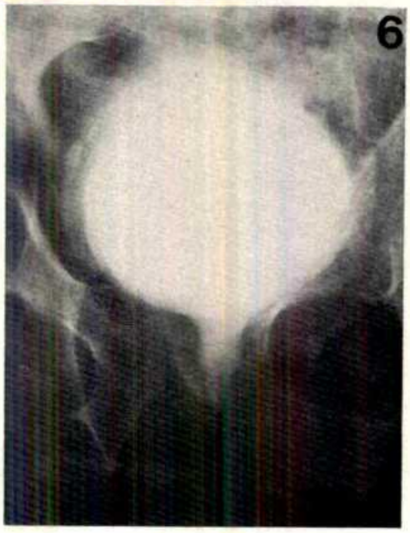
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In the presence of rather weak detrusor activity this detrusor sphincteric imbalance may be sufficient to prevent voiding altogether (Fig. 8). More commonly the imbalance results in incomplete bladder emptying with high residual urines (Figs. 9 and 10). The functional obstruction produced by detrusor sphincteric imbalance may lead to a high pressure voiding system (Fig. 11).

Not only does the degree of detrusor-sphincteric imbalance vary between individual patients it also changes over the months following injury in individual patients (Figs. 12 to 14).

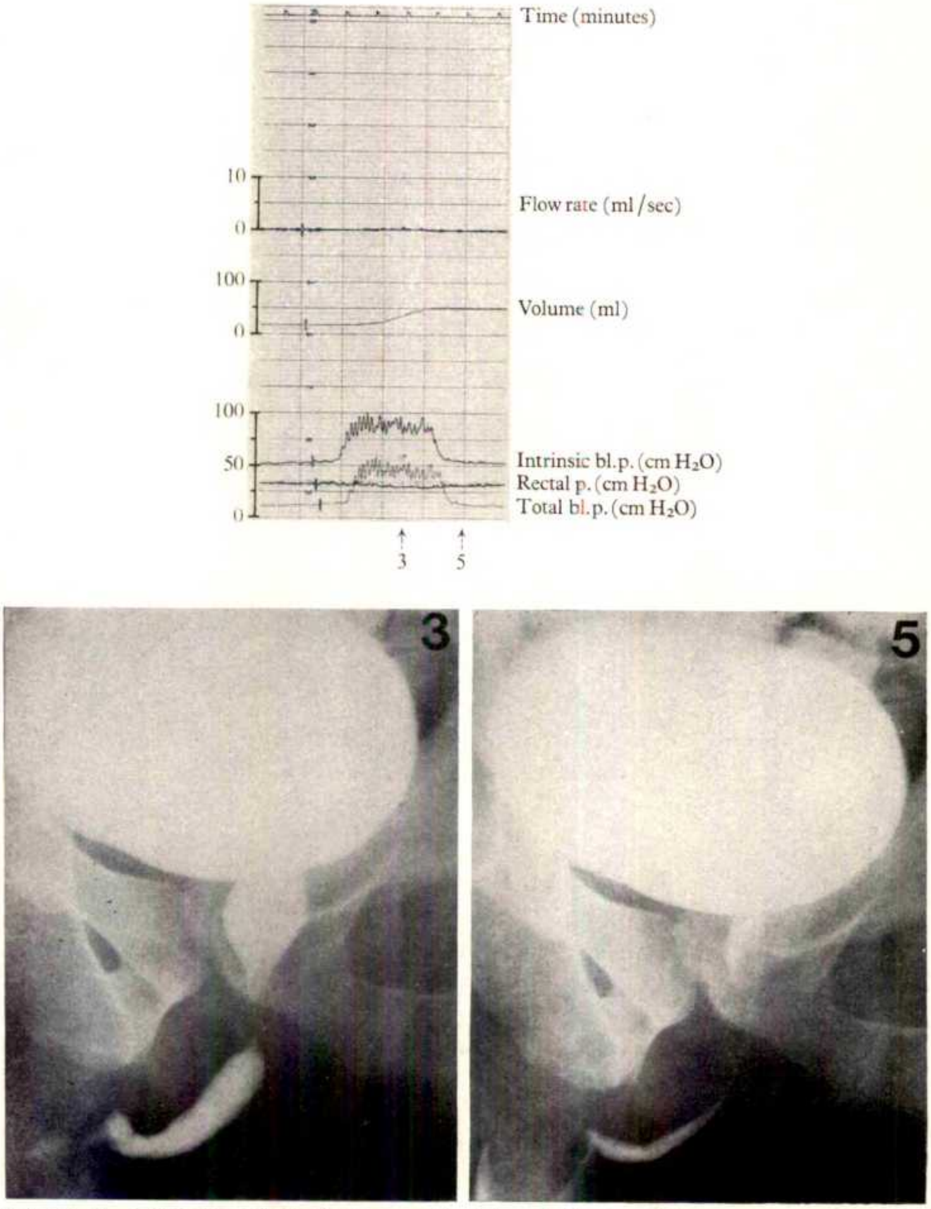

Fig. 15. Male, age 34, complete paraplegia D.6. 9 years after injury. Reflex rise of detrusor pressure (50 cm H_2O). Delay in onset of voiding. Very low flow rate (less than 1 ml/sec) with spasm of the external sphincter (X-ray 3). Incomplete bladder emptying.

Even in patients with low residual urines detrusor sphincteric imbalance is a constant feature. In these patients the bladder can be virtually emptied by reinforcing the detrusor contraction by tapping the lower abdominal wall, thus overcoming the functional obstruction at the external sphincter.

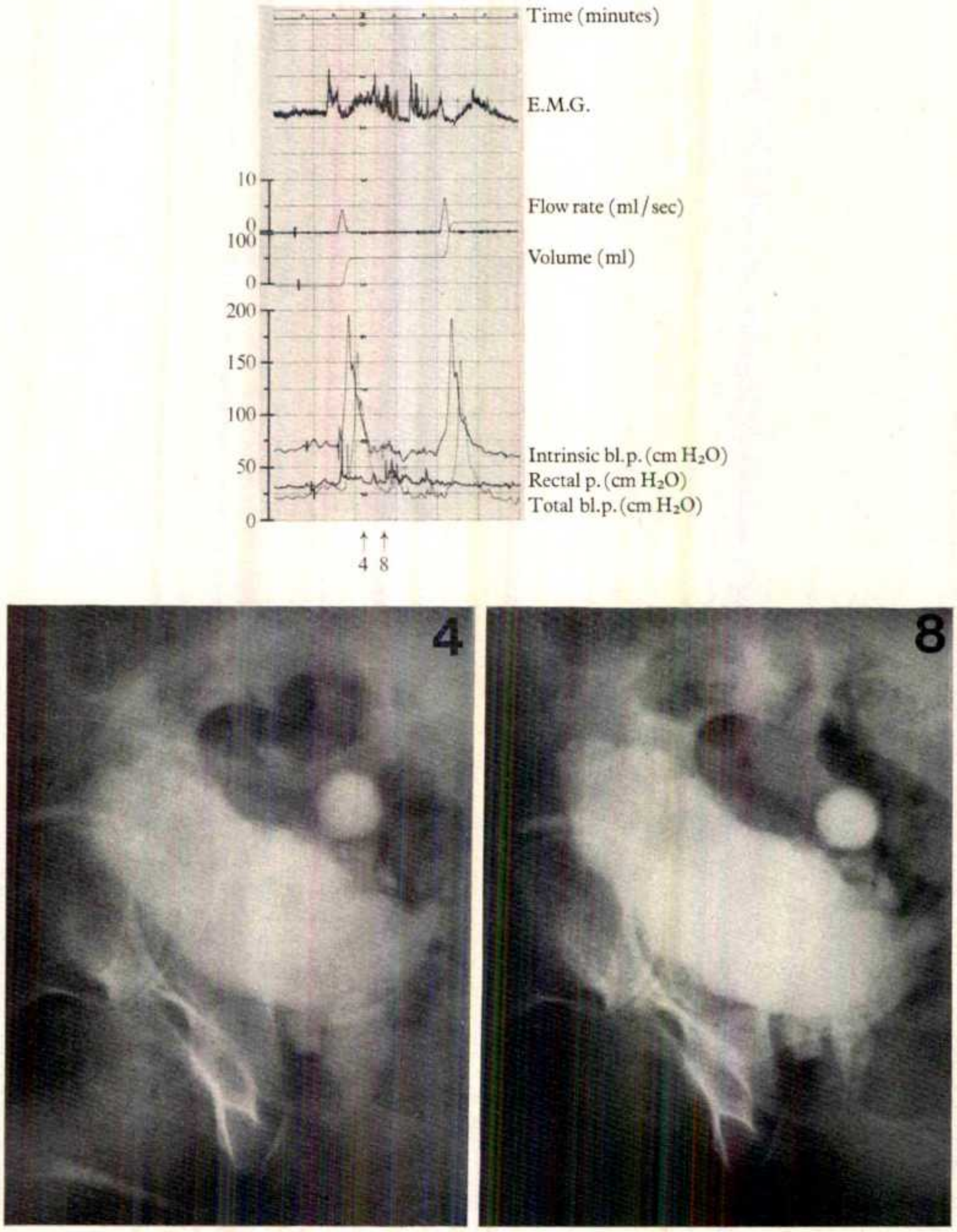

Fig. 16. Male, age 30, complete quadriplegia C.5. 5 years after injury. High pressure (145 cm H_2O) detrusor activity with increased pelvic floor EMG. Rapid fall of detrusor pressure. Considerable functional obstruction at the external sphincter (X-ray 4). Bladder neck wide open even when detrusor pressure returned to basal level (X-ray 8). High residual urines with upper tract dilation.

(b) *Long-Standing Reflex Detrusor Activity*

Marked detrusor-sphincteric imbalance may persist for many years and is not just a feature of the early recovery period (Fig. 15).

Another feature seen in long-standing patients with reflex micturition is a high-pressure voiding system with marked pelvic floor activity during voiding. Often the reflex detrusor activity is short-lived and may represent reflex inhibition of the detrusor from spasm of the external urethral sphincter. These short-lived detrusor contractions together with external sphincter spasm are insufficient to empty the bladder and are seen in long-standing patients with persistently high residual urines with or without upper tract reflux or dilatation (Figs. 16 and 17).

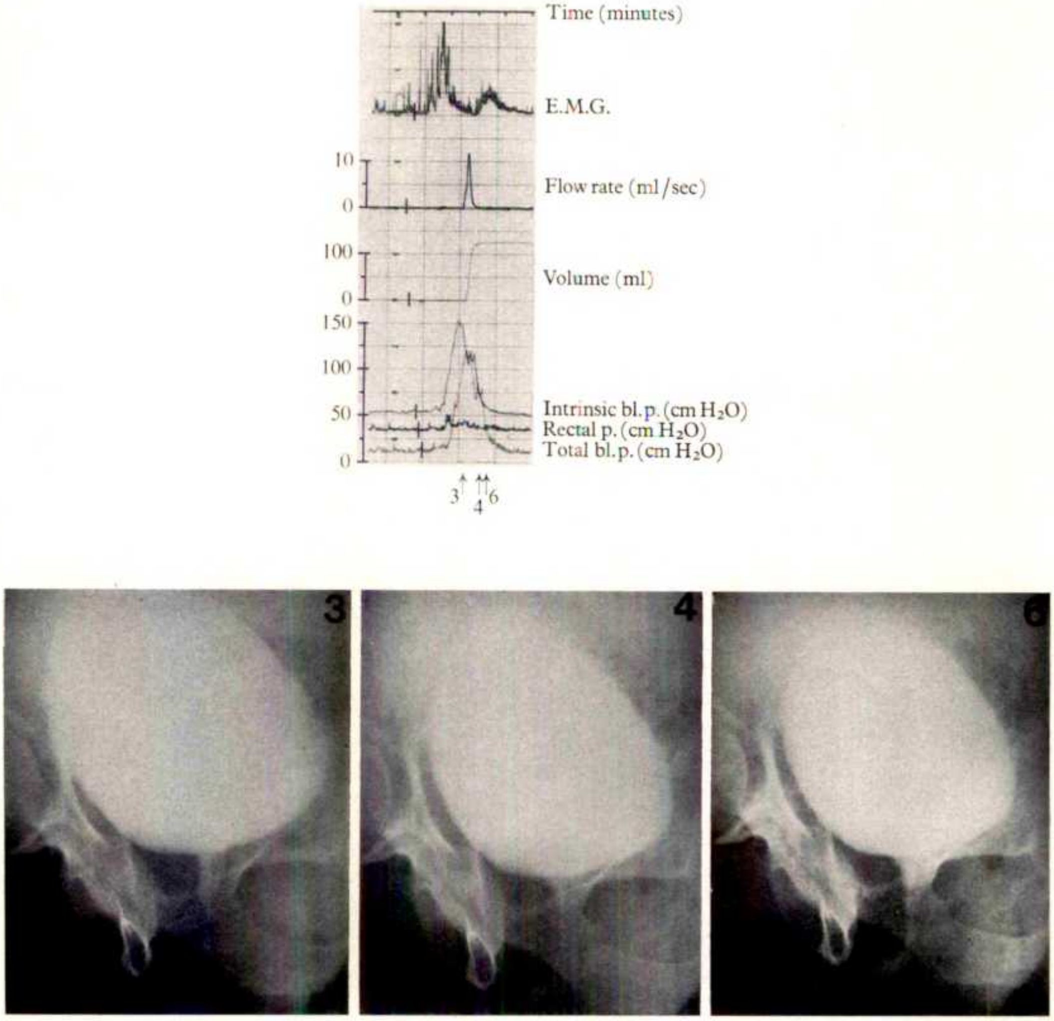

Fig. 17. Male, age 36, complete paraplegia D.5. 16 years after injury. Reflex rise of detrusor pressure (105 cm H_2O) with marked increase pelvic floor EMG. Delay in onset of voiding with hold up at the external sphincter (X-ray 3). Poorly sustained detrusor activity giving rise to incomplete bladder emptying with high residual urines.

Discussion and Conclusions

From our initial observations 2 main features emerge.

1. In patients with reflex bladders there is always evidence of detrusor-sphincteric imbalance even in patients with low residual urines.
2. There is often a continual changing pattern of reflex detrusor and sphincteric activity in the months and years following spinal injury.

The urological complications of urinary tract infection, and upper tract dilatation with or without reflux, are all related to the altered physiology of the bladder. Transurethral surgical procedures are designed to reduce the amount of residual urine by lowering the outlet resistance. It may be, however, that there are urodynamic features present which lead to upper tract complications even in patients with low residual urines. Only a continuing urodynamic assessment of patients with reflex micturition will allow us to assess the importance of the altered urodynamic state of the bladder in the production of upper tract complications.

Already we believe that urodynamic studies have assisted in the establishment of criteria for transurethral surgery, and in particular the assessment of the results of transurethral sphincterotomy.

Both over-distension and infection damage the detrusor which in turn can alter the reflex detrusor activity. These facts coupled with the observations of a changing pattern of reflex activity following injury makes continuous urological assessment of paramount importance in the long-term management of the spinal injury patient.

Summary

A method of the urodynamic investigation of paraplegic and quadriplegic patients is described.

Serial measurements of the urethral pressure profile in patients with developing reflex micturition demonstrate a rising pressure at the external urethral sphincter with time following spinal trauma.

Patterns of micturition with detrusor-sphincteric imbalance are described in patients with both early and well-established reflex micturition.

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Bates, C. P. and Corney, C. E. (1971). Synchronous cine-pressure-flow cystography: a method of routine urodynamic investigation. *British Journal of Radiology*, **44**, 44-50.

We wish to thank our colleagues Dr. A. G. Hardy and Dr. N. Watson (Spinal Injuries Unit, Sheffield) and Mr. J. L. Williams (Department of Urology, Sheffield) for their constant help in this work. The patient assistance of Mr. A. Tunstall and members of the Department of Photography is much appreciated.

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Unilateral Multicystic Kidney and Contralateral Hydronephrosis in the Newborn

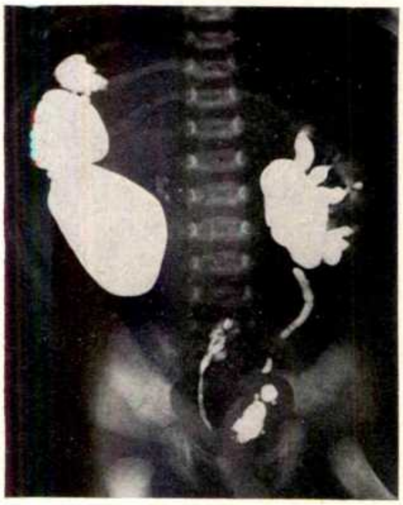
In 1936 Schwartz described for the first time an unusual unilateral multicystic kidney in a male infant, aged 4 months. Since then this condition has been described in several other reports. It was thought that the opposite kidney was always normal. Innes Williams (1958), however, found in one of his cases a partial atresia of the opposite ureter which had caused severe hydronephrosis.

Recently we saw a newborn with a unilateral multicystic kidney and a severe hydronephrosis of the opposite ureter, which closely resembled the patient mentioned by Innes Williams.

Case Report

A 12-year-old girl was sent to our hospital because of anuria, vomiting and a palpable mass in the right loin. During the first week after birth there were no feeding problems and apparently there was a normal urine output. On palpation there were extensive nodular masses in the flanks. Blood urea and creatinine were considerably raised (urea 251 mg%, creatinine 6·5 mg%) and there was also a severe acidosis (pH 7·20, Base Excess—16). There was pronounced oliguria. Because of the impairment of renal function with anuria, intravenous pyelography could not be done. Infusions with glucose 5% and sodium bicarbonate 4·2% were started, and cystography was performed. There was no vesico-ureteric reflux and therefore retrograde pyelography was indicated. On monitoring we saw bilateral slender ureters but visualisation of the pyela was impossible. The right ureter was displaced towards the midline. Because of a temporary fault in the apparatus X-rays could not be taken. Next the mass in the right flank was punctured and 10 ml clear yellow fluid was obtained and replaced by contrast medium. On monitoring, a cyst was seen. Further several cysts were punctured and emptied. The left kidney was not punctured as we assumed that there were bilateral multicystic kidneys in which case the prognosis was very poor. Afterwards there was a temporary production of urine but the acidosis remained unchanged and the child died after four weeks.

At autopsy the right kidney showed cystic enlargement and measured 10×5×4 cm. There was no communication between the several cysts, which measured up to 5 cm in diameter. The distal part of the right ureter was normal, but the proximal part was atretic. A normal cortex and medulla were not seen



The left kidney measured 6×3×2 cm, and the surface was smooth with some subcapsular cysts up to 0·3 cm. Post-mortem pyelography showed that the pelvis was dilated and there was a stenosis at the pyelo-ureteral junction. The rest of this ureter was normal. On cut surface the cortex, medulla and the number of calices were normal. There was no right or left sided uretero-vesical stenosis.

Comment

In view of the autopsy findings, the child could perhaps have been saved by a temporary pyelocutaneostomy. It was an error to assume that the left kidney was also a multicystic kidney. In the event of such an unusual case of a multicystic kidney, it is imperative to examine the opposite kidney carefully in case there should be a possibility to treat the associated anomaly.

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British Journal of Urology (1975), **47**, 177–183

A Clinical Evaluation of Hydrostatic Pressure Treatment for Carcinoma of the Bladder

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A study of the treatment of carcinoma of the bladder by hydrostatic pressure techniques has been carried out to try to confirm the findings reported by Helmstein (1972). This has been a purely clinical study carried out in the course of the routine management of the patients.

Patients and Procedures

Initially patients were selected either because of failure of local per-urethral methods to control their tumours adequately, or because their tumour was such that these local methods were deemed inappropriate. Such patients were selected for a more radical treatment such as external total dose radiotherapy, or a combination of radiotherapy and radical cystectomy. It was considered that a course of hydrostatic dilatation was justified in these circumstances, as, if successful, these more radical procedures may be averted, or postponed, and if unsuccessful they would still qualify for the treatment already selected. This did however naturally involve a delay whilst hydrostatic dilatation was performed and assessed, and during this period a very close surveillance was maintained.

In addition the patient had to be able to cooperate, be free from chronic respiratory disease likely to cause severe dyspnoea, CCF, or coughing, and be able to lie reasonably still for a 6-hour period.

The technique of Helmstein (1972), was followed meticulously.

Anaesthesia. The procedure was carried out under epidural anaesthesia, with a catheter maintained *in situ* during treatment, using 1·5% lignocaine, or 0·5% marcaine, both with 1 : 200,000 adrenalin. Additional quantities were given immediately any return of sensation was detected.

Both the solo Foley catheter, and the balloon techniques were used.

1. *Foley catheter technique*

A 22F triple lumen Foley catheter, with a 30 cc balloon was introduced into the bladder. One limb was connected to a container of sterile 0·9% saline, suspended from a drip-stand capable of considerable elevation, and the other open limb, to a manometer. The saline, to which was added 100 ml sodium diatrizoate 45%, plus 10 ml methylene blue, was then allowed to run into the bladder until the intravesical pressure recorded on the manometer reached the diastolic blood pressure. During the inflation procedure, the bladder was screened radiologically to detect either ureteric reflux, or unsuspected diverticula. Both of these were considered to be indications either for discontinuing the procedure, or changing immediately to the intravesical balloon technique.

The Methylene blue was added to the fluid purely as a dye to add to the ease of reading the manometer line.

2. *Balloon technique*

This differed from the above in that a rubber balloon was tied to the end of the triple lumen catheter, and then introduced into the bladder in the same manner as used by Helmstein. The balloons used were of the children's toy variety, spherical, and were tested and found to fill to an excess of 7 litres prior to rupture. The elastic recoil of the balloon was found never to exceed 30 mm Hg, and was usually in the region of 25 mm Hg. Sterilisation was achieved by immersion in chlorhexidine solution, inside and outside the balloon, and appeared entirely satisfactory.

When attached to the catheter, the 2 open channels both opened inside the balloon, and were connected to a similar reservoir of 0·9% sterile saline, containing 10 ml methylene blue, but no radio-opaque contrast medium;

and the manometer. Using the balloon the fluid was in a closed system, so X-ray screening was omitted during inflation as ureteric reflux could not, of course, occur. The danger from any small diverticulum which had been missed on previous excretory urography and cystoscopy was thought to be negligible.

The bladder was then subjected to hydrostatic dilatation for 6 hours. Without a balloon the intravesical pressure was maintained at the diastolic blood pressure throughout, with an upper limit of 100 mm Hg. When the balloon was used the manometer pressure was maintained at the diastolic blood pressure+30 mm Hg to allow for the elasticity of the rubber. This allowed for a manometer reading of 130 mm Hg as the upper limit.

In most instances a member of the medical team was present with the patient throughout, to enable the epidural anaesthetic to be topped up immediately if necessary, and to monitor the patient's blood pressure and adjust the intravesical pressure accordingly. In addition, as reported under complications below, there were often other factors occurring during the procedure requiring prompt judgement and attention. For the 6 hours the patient was permitted occasional sips of water only.

At the end of the period the catheter, together with the balloon if used, was withdrawn, and replaced with a large Simplastic Foley catheter which was left on continuous drainage for a minimum of 48 hours. During this period it was noticed that considerable debris drained from the bladder.

Results

These are shown in the accompanying Table (pp. 180-181), together with any relevant previous history.

14 patients had a full, single, 6-hour course of treatment. Three, (nos. 3, 4, and 13) were abandoned; nos. 4 and 13 because of bladder rupture, and no. 3 because of free reflux up both ureters at a time when we were not in a position to establish immediately a change to the balloon technique. Because of the aggressive nature of this man's tumour, we did not procrastinate further, but proceeded to total radical cystectomy.

We have not yet become aware of producing any morbidity in these patients even after vesical rupture. Both patients who suffered this complication have been followed up for over a year to date.

Complications

1. Vesical rupture

In 2 patients, (nos. 4 and 13—both with extensive tumours invading muscle (T2)), rupture of the bladder during this procedure occurred—one with the balloon technique and the other without. In 1 patient (no. 4), the bladder ruptured after 30 minutes and the procedure was terminated. The bladder was repaired, and the prevesical space and bladder were drained. He had shown no signs of incomplete anaesthesia at the time. However, in retrospect, he did admit to some return of sensation prior to the catastrophe. We found invariably that there was a detectable rise in intravesical pressure when the effects of the epidural anaesthetic were waning; however in this case we thought this was an unlikely event so soon after the start of the procedure, and induction of the epidural anaesthetic.

The other patient (no. 13), ruptured the bladder after 3½ hours. He had become restless, and was given i.v. diazepam by a doctor inexperienced in managing these particular patients, and to whom the potential dangers of sedation were not known. He then slept, and shortly afterwards the bladder ruptured, without any warning of return of sensation. However, again in retrospect, this may well have been the underlying cause of the initial restlessness.

We have found that it was dangerous to give any sedation to our patients as their full mental cooperation was required to detect any lack of anaesthesia. If this occurred the consequent rise in intravesical pressure was followed so swiftly by rupture, that this situation was avoided if at all possible.

2. Ureteric reflux

This was of significance only in non-balloon procedures. One patient, no. 3, is reported above, and the only other patient to show this, no. 5, was immediately changed to a balloon technique.

During the 6-hour inflation, it was common for most of the patients to experience loin discomfort, which, in a few, amounted to pain. With the bladder inflated, there is obviously no ureteric drainage and consequently, as the kidneys continue to excrete, there is a pressure build-up in the system proximal to the bladder. We did not find any complications from this period of obstruction, nor from the rapid decompression which followed at the end of the 6 hours.

3. *Urethral leakage*

This was a problem in all non-balloon procedures. It was controlled with difficulty by varying the amount of water in the catheter balloon together with traction on the catheter to obtain as snug a fit as possible into the bladder neck. On no occasion was it serious enough to prevent the intravesical pressure being maintained, but a constant inflow of fluid was often required, and the procedure then became somewhat unpleasant for the patient due to constant urethral leakage.

4. *Balloon rupture*

In 1 case (patient no. 14), we found that the balloon ruptured within the bladder during the procedure. This became apparent when urethral leakage occurred stained with methylene blue. The bladder was intact, and the procedure was completed as for the non-balloon method. There were no demonstrable ill effects, and the balloon was retrieved on the end of the catheter *in toto*.

5. *"Autonomic imbalance" effects*

The exact mechanism of these distressing side effects is uncertain. 30% of the patients suffered nausea, retching or vomiting, sweating and generally felt wretched; this was accompanied by facial pallor, and on occasions, bradycardia and hypotension. Whether this was an effect of the gross bladder distension, or the epidural anaesthetic agents is not clear.

It was found that the bradycardia could be controlled with atropine.

Once these side-effects were recognised, and their response to atropine elucidated, an atropine premedication 0·6 mg, was routinely given, but nothing else. However, even then, bradycardia and nausea still occurred, and a further dose or doses of atropine would be required.

Perphenazine 5 mg was used sparingly for severe and distressing nausea, if this persisted after the administration of atropine.

Discussion

Although it is too early to make any reasonable deductions regarding their eventual outcome 4 out of 14 patients who had a complete course of hydrostatic dilatation have been free of further demonstrable tumour at 12 months. None of them had previously achieved during their routine 3-monthly check cystoscopies, more than 1 visit in succession where no tumour was found. These 4 patients had been followed-up for periods ranging from 10 years to 33 months after presentation. Therefore a small but real improvement in their bladder situation has been achieved so far, at no cost in morbidity.

3 of these patients had well differentiated carcinomas, grade 1 histologically. 2 of them were classed as T1, and the other T2. The 4th was a focally anaplastic tumour, although still T1, the type of tumour histologically that Helmstein found did best. In this small series, of those patients who had a complete course of treatment, 1 out of 2 histologically grade 3 tumours, and 3 out of 12 grade 1 tumours responded fully, and remained free of tumour at 1 year. However, with regard to the depth of invasion, 1 out of 7 T2 tumours and 3 out of 7 T1 tumours responded fully and remained tumour free at 1 year. With such small numbers no conclusions can be drawn from these statements, but the table of results is appended in detail so that these patients can be compared with, and incorporated into any other series of patients who have been identically treated.

With regard to the patients who failed to show any improvement several features are apparent.

Pt	Date of Diagnosis	Tumour	Histology	UICC Class	Previous Treatment	Outcome	Histology	Date of Dilatation	Type	Outcome	Histology	Further Treatment
1. T.P.	26/4/1968	4 × 2.5 cm flat ulcer proximal to RUO with altered surrounding mucosa	Mod. Diff. TCC	T2	Gold grains	Continuous new tumours	Residual Ca. cells in irradiated bladder	28/7/72	NB	Slough over bladder persisting to Oct. 1973 but slowly clearing	Possible malig. cells persist	Close observation and EUA's
2. E.B.	12/4/1972	Small papillary lesion plus diffuse villous mucosal change over base and around both UO's	Well diff. TCC	TIS	Intravesical Thiotepa, 30 mg × 2 and Fulguration	Continual new tumours	Well Diff. TCC	4/8/72	NB	One area of solid tumour, other areas of stunted villous mucosal change	Well diff. TCC	DXT
3. W.C.	12/5/1972	Widespread papillary and solid tumours	Poorly diff. TCC	T2	DXT	Slight improvement only		16/8/72	NB	Free reflux up both ureters procedure abandoned	Well diff. TCC	Radical cystectomy
4. E.T.	18/8/1972	Mainly solid with areas of papillary tumour 4 cm diam. on base and around both UO's	Well diff. TCC	T2	None			23/8/72	NB	Bladder ruptured		TUR, and Fulguration
5. R.McK.	20/8/1969	Papillary and solid TCC above LUO and extending submucosally	Well diff. TCC	T2	Gold grains, Fulguration Thiotepa	Further widespread tumour	Well diff. TCC	25/8/72	NB to B	11/72 Low pap. lesions over vault June '73. Further papillary lesions	Carc. in situ Well diff. TCC (T1)	Fulguration Fulguration
6. D.M.	Nov. 1965	Single 4 cm villous tumour	Well diff. TCC	T1	TUR & Fulguration	Well controlled until 1972. Then multiple villous tumours	Invasive well diff. TCC	20/9/72	B	Much improved fewer and better defined villous tumours	Well diff. TCC(TIS)	Fulguration
7. S.W.	Mar. 1971	3 cm necrotic calcified, sessile tumour, with surrounding villous tumours	Well diff. TCC	T2	DXT. & later fulguration	Bleeding altered mucosa with stunted villous tumours	A typical transitional cells highly suspicious of Ca (T1)	22/9/72	B	No further tumours to 3/7/73		
8. A.S.	May 1969	Multiple papillary lesions to 2.5 cm diam. base, with numerous satellites	Mod well diff. TCC	T1	Fulguration	Well controlled to June '72, then more and more papillary tumours	Focally rather anaplastic carcinoma (T1)	22/9/72	B	No further tumours to 31/8/73		

B = Balloon technique. NB = Non-balloon technique.

9. J.T.	Feb. 1962	Solitary papillary tumour followed by continual widespread further tumours in large numbers	Well diff. TCC	T1	Fulguration Thiotepa Epodyl	Control increasingly difficult	Well diff. TCC	Sept. 1972	B	Increasing nos. of widespread mucosal tumours	Well diff. TCC	Fulguration Thiotepa probably for DXT
10. J.O'L.	July 1963	Villous papillary tumour	Mod. well diff. TCC	T1	Fulguration	Multiple further tumours	Well diff. TCC (T1)	14/10/72	B	No further tumours to Oct. '73		
11. P.H.	Nov.1970	5 cm villous tumour around RUO	Well diff. TCC	T1	Fulguration later required Thiotepa	Multiple new tumours	Well diff. TCC	18/4/72	B	No improvement	Well diff. TCC	Further fulguration and Thiotepa
12. W.S.	Jan. 1970	3 Papillary tumours beyond LUO	Well diff. TCC	TIS	Fulguration later, Thiotepa	Controlled to Oct. '71, then increase in size	Well diff. TCC invading sup. muscle	20/10/72	B	No further tumours to 8/10/73		
13. G.P.	Nov. 1972	Large villous tumour involving both UO's and bladder neck	Well diff. TCC	T2	None			17/11/72	B	Much reduced area of stunted mucosal change Bladder ruptured after 3½ hours	Unsatisfactory	Thiotepa × 2 5/9/73 No further growth
14. C.C.	Jan. 1973	4 cm solid and necrotic tumour around RUO	Poorly diff. TCC	T2	None			5/2/73	B and NB	Necrotic tumour	Some viable anaplastic cells present	DXT
15. H.B.	Feb. 1972	Single, solid and villous tumour 4×4 cm above LUO	Well diff. TCC	T2	None			13/2/73	B	Main tumour unaltered and many new pap. growths	Well diff. TCC	DXT then radical cystectomy
16. A.H.	July 1972	3 cm diam. vault tumour	Well diff. TCC	T2	DXT	Rapid progress to widespread metastases	Well diff. TCC	6/3/73	B			Died 23/3/73 carcinomatosis from ca. bladder
17. K.B.	Feb. 1972	Treated elsewhere with DXT										
	Mar. 1973	Resistant tumour above RUO	Mod. well diff. TCC	T2				20/3/73	B	More extensive tumour	Mod. well diff. TCC	Radical cystectomy

B = Balloon technique. NB = Non-balloon technique.

Firstly, they all had tumour present at their first check cystoscopy, normally 3 months after the dilation. None of them was clear at any time, in contrast to the successes, none of whom has shown any further tumour to date. Over a 12-month period of follow-up, we have not observed any patient to be initially clear, and then to develop tumour. Secondly, although in these patients tumour was still present, in several it was much less extensive, and the bladder appeared cleaner and healthier. Helmstein found that a second dilatation was beneficial in some patients where a partial improvement had been achieved initially. We have not as yet done this as 30% of the patients found the procedure something of an ordeal, and coincidentally this included those for whom a second treatment might have been beneficial.

Patients 1 and 13 deserve special mention. Patient 1 had unequivocal carcinoma cells in his bladder following treatment of his T2 tumour with interstitial gold grains. After hydrostatic dilatation, follow-up biopsies have shown only very dubious malignant cells in an area subjected to prior irradiation. He has been followed up for 15 months, and the clinical picture has during this time continually improved in a very fit man. It may well be that time will place him also amongst the successes. Patient 13 had a large T2 tumour and during treatment his bladder ruptured after 3½ hours. At follow-up a much reduced area of stunted mucosal change was found, totally unlike the original tumour. It was unfortunately not biopsied at this time, and Thiotepa was instilled. Since that time he has been entirely free of any signs of tumour for 1 year. The omission of the biopsy unfortunately precludes our placing him in the category of success, and it is possible that the tumour was eradicated by the Thiotepa. Incidentally there is no evidence of any dissemination of tumour in this patient in spite of his bladder having ruptured.

Bubenik *et al.* (1970*a*, 1970*b*), working with the same group in Stockholm have found evidence that a cell-mediated immune response is initiated by hydrostatic bladder dilatation, and that specific cytotoxic lymphocytes could be demonstrated from patients so treated. In addition, complement dependent antibodies were identified in some 60% of their patients after treatment. This work prompted us to attempt this treatment in patient 16, whose transitional cell carcinoma had progressed to the stage of widespread skeletal and soft tissue metastases. We obtained no improvement either objectively or subjectively, and the patient died a few weeks later. In this instance there was obviously a huge bulk of tumour in the patient, the control of which was not reasonably anticipated.

The impressions gained by comparing the 2 techniques used to establish intravesical dilatation, namely with or without a balloon, have led us to conclude that in our hands the balloon technique is the easier to control. Radiological screening during inflation is not considered necessary and urethral leakage does not occur. The introduction and removal of the balloons on the catheter occasioned no difficulty. Although a random sample of each batch of balloons was tested for capacity, the balloons actually used for treatments were not previously inflated, and so small flaws were not detected by the superficial inspection they received. This, on one occasion, produced an intravesical rupture with no ill effects. Any large flaws were of course noticed and such balloons were discarded.

Conclusion

We think that we have sufficient evidence to show that this technique is another clinical tool of value in the management of patients with transitional cell carcinoma confined to the bladder; and that this small series of relatively short duration does confirm the earlier work of Helmstein.

We are not able to suggest any criteria for patient selection other than that which we included in the relevant section. There is still no evidence of which we are aware, that success has been achieved in treating tumours in excess of T2, or with metastases. All our experience, and also that of Helmstein so far reported, has been confined to transitional cell carcinomata.

We have no evidence of any lasting morbidity associated with this procedure, even after vesical rupture; nor of any deterioration in the clinical state of any patient on whom it has been performed. We feel it is greatly on the credit side that the patients who have responded still have their bladders and have not required radiotherapy. We will have to wait longer however, to see if this optimism is justified.

Summary

A small clinical series of patients treated by hydrostatic bladder dilatation is reported.

The methods used, the complications and technical difficulties encountered are described.

4 patients out of 14, who had a complete course of treatment are free of any further tumour 12 months later, which in the context of their previous progress is a considerable improvement. These 4 patients did not appear to have any particular feature which, on clinical assessment, would have allowed us to be more selective in applying this treatment.

I wish to thank Mr P. F. Philip, MS, FRCS, for permission to report these patients who have been under his care, and for his encouragement whilst this investigation has been carried out.

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Fibrosarcoma arising in Diverticulum of the Urinary Bladder

Malignant connective tissue tumours of the urinary bladder form 0·5% or less of total vesical malignancy (Wallace, 1959). Those primarily arising in diverticula constitute an extreme rarity. A meticulous search through the literature reveals stray, rather poorly documented examples of "sarcomas" of urinary diverticula.

We report a fibrosarcoma of a bladder diverticulum, which we believe to be the first reported in the literature.

Case Report

A Hindu male aged 68 years presented with bouts of haematuria and dysuria. Pyelogram detected a large diverticulum involving the left side of the bladder wall with poor dye concentration in the left kidney. At operation, a firm, freely mobile mass was seen to fill up the diverticulum. A complete resection of the diverticulum and the tumour with Y-V plasty repair was carried out. The tumour recurred 16 months after the operation when the urine analysis showed large numbers of red blood cells. In addition, 2 metastatic nodes were detected in the left rectus abdominis. The recurrent and metastatic tumours were excised. 16 months later, the patient was re-admitted in an extremely cachetic, deeply comatose condition with a large nodular mass in the abdominal wall and died a day later. No autopsy was performed.

Pathological Features

The tumour removed at the first operation consisted of a large, protuberant mass measuring 10 × 5·5 × 5 cm, arising from the wall of the diverticulum. The surface was coarsely papillary and polypoid with deep furrows intervening between the projections. Cut section was glistening white and fibrillar. No involvement of the wall of the diverticulum was observed.

Microscopic examination revealed a highly differentiated fibrosarcoma composed of spindle-shaped cells with tapering nuclei separated by an abundant collagenous tissue Extensive hyalinised acellular areas were also present. Foci of increased cellularity, plump nuclei and mitoses indicated the malignant nature of the tumour. The tumour was covered by an intact metaplastic, keratinising stratified squamous epithelium. (Fig.).

The recurrent and metastatic tumours were firm, smooth, masses measuring respectively 5 × 4 × 3 cm, 3 × 2·7 × 2·5 cm and 1 × 1 × 0·7 cm. The histology was similar to the primary tumour except for extensive areas of myxomatous degeneration associated with infiltration of the bladder wall.

Comment

Neoplastic change in vesical diverticula is a well-recognised complication, almost 3% of diverticula revealing presence of a tumour (Wallace, 1959). In a patient with both diverticulum and vesical tumour, the chances that the tumour is located in the diverticulum are very high (Knappenberger *et al.*, 1960).

Treatment is essentially surgical, since the tumour is usually radioresistant. Results of treatment are worse as compared to bladder tumours without diverticula (Ashton Miller, 1958), the thin fibrous wall of the diverticulum facilitating early invasion.

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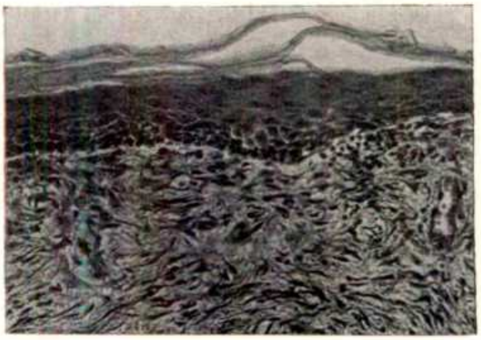

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The Distribution and Retention of Cadmium 115m in the Rat Following Injection into the Prostate

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Injection of cadmium into the rat produces gonadal changes which are well documented (Parizek and Zachar, 1956; Gunn, Gould and Anderson, 1961). According to Gunn, Gould and Anderson (1967), direct injection of cadmium into rat prostate produces no histological changes, which differs from recent experience (Scott and Aughey, in preparation) in which changes were found when the various prostatic lobes were injected directly. In the latter case, at least, some local retention of cadmium might be an essential corollary accounting for the histological and ultrastructural changes observed. Apparently, such retention has not been reported previously and the present study had the limited aim of investigating this facet.

Material and Methods

30 healthy adult male Wistar rats approximately 100 gm weight fed on laboratory chow, *ad libitum*, were used.

In the first experiment 18 rats were injected with 22·4 μCi ^{115m}Cd (equivalent to 0·075 mg Cd) 9 of them into the left ventral prostate and the other 9 into the left dorsolateral prostate using the surgical procedure already described (Scott and Aughey). 3 animals from each group were killed at 1 day, 21 days and 42 days after injection and monitored immediately after death to determine the total amount of isotope in the body using, for convenience, a mobile whole-body radioactivity monitor (Boddy, 1967). The amount of ^{115m}Cd in the right and left ventral, right and left dorsolateral lobes of the prostate, the lower pole of the kidney and testis was then determined using a well-type sodium iodide detector. Each organ sample was weighed individually, and maintained in ice-cold buffered 0·32 mol/l sucrose before counting.

In the second experiment, 12 rats were injected with 18·5 μCi ^{115m}Cd (equivalent to 0·044 mg Cd) 6 of them into the left ventral lobe and the remaining 6 into the left dorsolateral lobe of the prostate. 2 rats from each group were killed at 1 day, 21 days and 42 days after the injection and monitored for total body retention of ^{115m}Cd. From the 2 rats in which the ventral prostate was injected the separate right and left ventral lobes and the dorsolateral lobes were dissected out. Corresponding lobes from both animals were then combined giving 3 samples. Each sample was homogenised on 0·32 mol/l sucrose buffer containing 3 mmol of $MgCl_2$ (Mangan, Neal and Williams, 1968). A similar procedure was followed for rats injected into the dorsolateral prostate except that the right and left dorsolateral lobes were taken to provide separate samples and the right and left ventral lobes were combined. After differential centrifugation, 3 fractions were obtained including whole cells + nuclei, a microsomal/mitochondrial fraction and a supernatant fraction. Each fraction was checked for accuracy by preparing pellets embedded in epon, and examining the section with the electron microscope.

Tissues for electron microscopy were processed and embedded in epon (Luft, 1961). Silver-gold sections were collected on coated grids and the Ilford L4 nuclear emulsion film deposited by the loop method (Caro, 1961). After exposure the film was developed and fixed, and the sections examined initially unstained, then after uranyl acetate staining.

Table I

Distribution of ^{115m}Cd activity in rat organ samples after injection into the ventral prostate

	^{115m}Cd Activity as % Total Body Activity ×100/gm Organ					
	Day 1		Day 21		Day 42	
Organ	Activity	Mean ± Stan. Error	Activity	Mean ± Stan. Error	Activity	Mean ± Stan. Error
Ventral prostate	283	546 ± 385	696	734 ± 234	242	144 ± 64
	51		350		168	
	1300		1160		22	
Dorso-lateral prostate	140	185 ± 112	56	138 ± 88	250	111 ± 72
	17		44		72	
	398		313		11	
Testis	7	7 ± 3	21	14 ± 4	7	11 ± 3
	3		10		17	
	11		10		9	
Kidney	49	55 ± 4	376	397 ± 61	368	360 ± 32
	62		304		302	
	55		511		410	

Table II

Distribution of ^{115m}Cd activity in rat organ samples after injection into dorsolateral prostate

	^{115m}Cd Activity as % Total Body Activity ×100/gm Organ					
	Day 1		Day 21		Day 42	
Organ	Activity	Mean ± Stan. Error	Activity	Mean ± Stan. Error	Activity	Mean ± Stan. Error
Ventral prostrate	13	38 ± 14	136	317 ± 122	43	75 ± 18
	13		548		105	
	59		267		76	
Dorsolateral prostate	64	80 ± 11	279	450 ± 204	33	118 ± 62
	75		215		240	
	100		856		80	
Testis	3	5 ± 3	53	41 ± 7	37	26 ± 6
	2		29		23	
	11		43		18	
Kidney	44	57 ± 8	557	368 ± 104	277	253 ± 13
	73		349		252	
	56		198		232	

Results

1. *Whole-body retention*

   The mean whole-body retention at day 1 and at day 21 was not significantly different, the respective mean value being 97·3% and 99·6%. The mean retention at day 42 was 87·3%.

2. *Retention by body organs*

   The results of measuring the ^{115m}Cd in prostatic tissue, kidney and testis are summarised in Tables I and II. To eliminate variations due to dispensing excretion, etc., the results were normalised to the whole-body retention.

Table III

Distribution of ^{115m}Cd activity in cell fractions of rat dorsolateral and ventral prostate

	^{115m}Cd Activity as % Total Body Activity × 100					
Sample	Day 1		Day 21		Day 42	
	a	b	a	b	a	b
Nuclear fraction						
1	85·3	245·6	30·0	61·5	36·5	83·2
2	1·5		4·3		3·0	
3	33·1		14·3		18·3	
4	125·7		12·9		25·4	
Microsomal/ mitochondrial fraction						
1	30·1	65·7	5·0	11·0	5·4	16·7
2	1·0		0·3		0·7	
3	2·7		2·2		5·6	
4	31·9		3·5		5·0	
Supernatant fraction						
1	34·8	92·4	32·6	78·4	63·1	203·8
2	2·7		8·4		11·1	
3	19·5		27·6		84·5	
4	354		9·8		45·1	

1. Combined right and left ventral prostate following injection ^{115m}Cd into left ventral prostate.
2. Combined right and left dorsolateral prostate following injection ^{115m}Cd into left ventral prostate.
3. Combined right and left ventral prostate following injection ^{115m}Cd into left dorsolateral prostate.
4. Combined right and left dorsolateral prostate following injection ^{115m}Cd into left dorsolateral prostate.

(*a*) *Left ventral prostate injection*

A highly significant amount of ^{115m}Cd was found in the ventral prostate at 1, 21 and 42 days post-injection. The mean values (Table I) correspond with a retention in the order of 1 to 5 μg Cd/g tissue. The levels did not change significantly with time ($p > 0·05$) but large variations from one animal to another were apparent, and probably obscured otherwise significant changes. Smaller, but readily detectable, amounts of ^{115m}Cd were found in the dorsolateral prostate, kidney and testis. The only significant change with time ($p < 0·05$) was the increase in the kidney level between day 1 and day 21. The concentration in the testis (μg Cd/g tissue) was lower than in the other tissues.

(*b*) *Left dorsolateral prostate injection*

As shown in Table II, the findings essentially correspond to those just described except that the increased concentration of ^{115m}Cd in kidney tissue between day 1 and day 21 was significant at only the 10% confidence limit, presumably the larger inter-animal variation was again a contributory factor to the uncertainty.

3. *Cell fraction determination*

The distribution of ^{115m}Cd among the cell fractions is summarised in Table III. Under each day, the activities of individual samples are given in column *a*. As would be expected, on

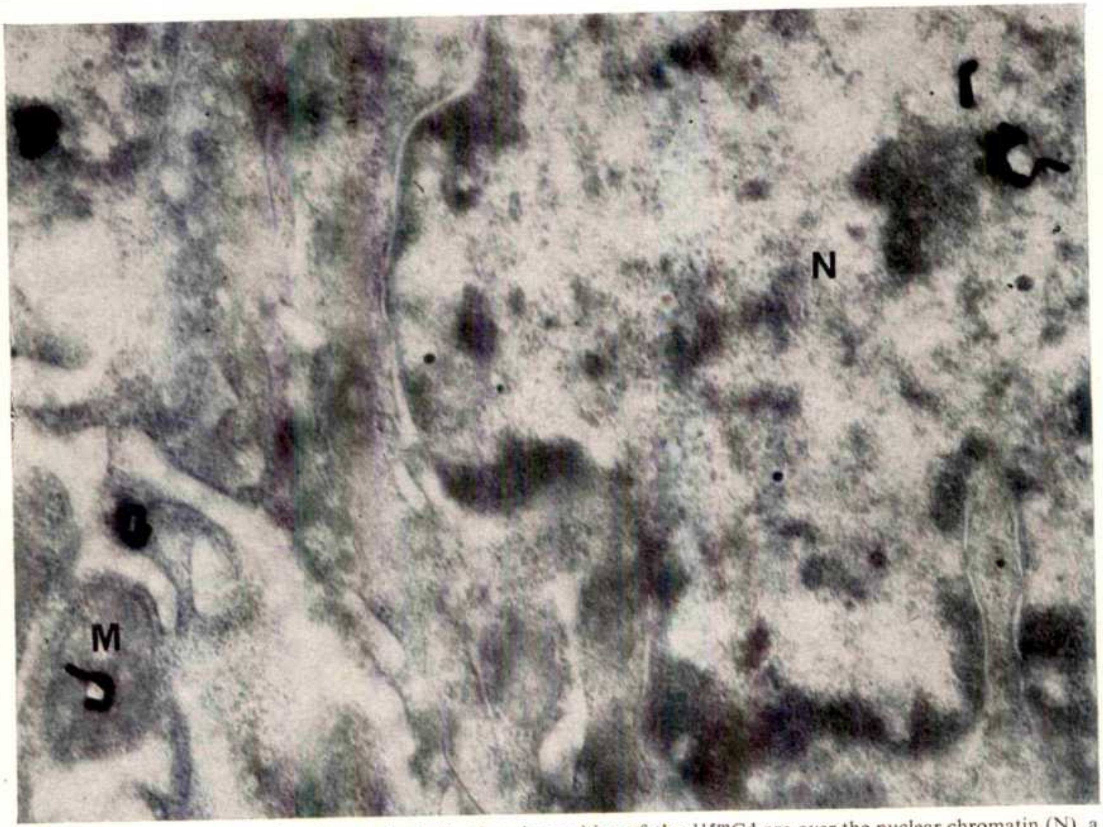


Fig. 1. Rat ventral prostate, the silver grains indicating the position of the ^{115m}Cd are over the nuclear chromatin (N), a mitochondrion (M) and scattered elsewhere in the cytosome. Autoradiograph. Uranyl acetate. × 30,000.

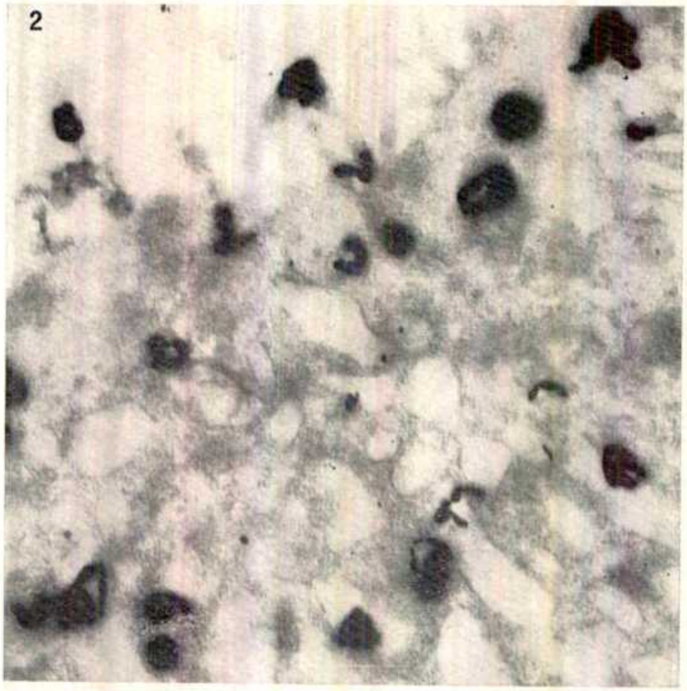
day 1, the highest levels of ^{115m}Cd were associated with the fractions from the respective sites of injection. However, there was suggestive evidence that the ventral prostate had a greater uptake in all fractions when the dorsolateral prostate was injected than vice versa. There was evidence also that this effect was accentuated with time, since from day 21 onwards, following injection into the dorsolateral prostate, the level of ^{115m}Cd in the ventral prostate was effectively as great or greater than that in the dorsolateral prostate. The converse was not observed. Column *b* of Table III represents the total ^{115m}Cd content of the cell fraction. Qualitative interpretation of these results suggested a general trend from the nuclear fraction to the supernatant, with a significant initial mitochondrial/microsomal fraction decreasing rapidly, over the period of the experiment.

4. *Autoradiography*

The electron micrographs shown in Fig. 1 illustrate the superimposition of ^{115m}Cd on the nuclear chromatin and in Fig. 2 on the lumenal cytosome and lumenal contents of the ventral prostate. The dorsolateral prostate shows a lesser degree of concentration and a total absence of ^{115m}Cd from small groups of cells, as demonstrated in Fig. 3. These findings reinforce the results from nucleonic counting.

Discussion

Whether or not cadmium injected into the prostate is associated with subsequent prostatic carcinoma is open to conjecture. Our findings (Scott and Aughey) suggest this is so, in contra-



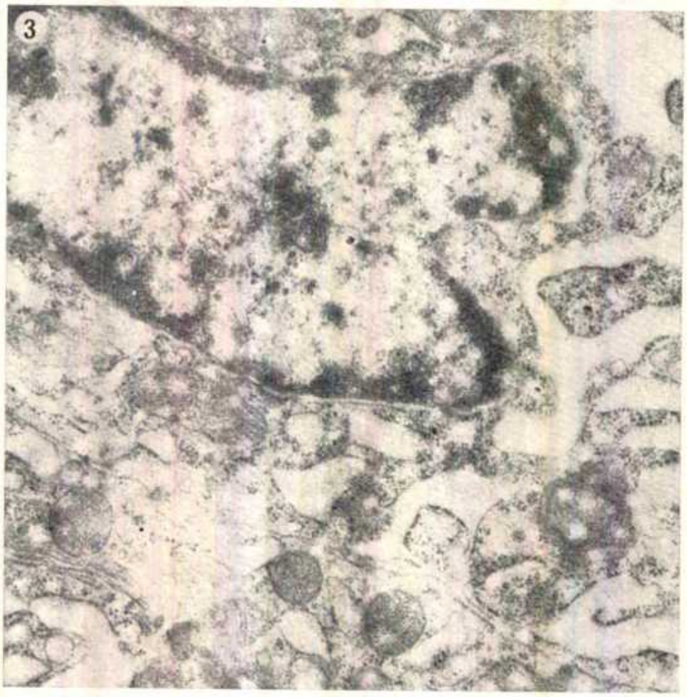


Fig. 2. Rat ventral prostate, illustrates the concentration of silver grains in the luminal cytosome, and in the secretion. Autoradiograph. Uranyl acetate. × 30,000.

Fig. 3. Rat dorsolateral prostate, to show the negative appearance of many of the parenchymal cells after exposure to ^{115m}Cd. Autoradiograph. Uranyl acetate. × 30,000.

diction of the negative observations of Gunn *et al.* (1967). For cadmium to act as a causal agent in these circumstances, some fraction of the injected dose must presumably remain in the gland.

The present experiments show that the rat prostate is capable of retaining cadmium in measurable amounts up to 6 weeks after initial injection and that the cadmium retention varies between the dorsolateral and ventral lobes of the prostate. The ventral prostate appears to have a greater affinity for ^{115m}Cd than the dorsolateral lobe which is interesting since the present authors have demonstrated squamous cell carcinoma of the ventral lobe after cadmium injection. Such a finding could be related to the high concentration of zinc in the dorsolateral prostate protecting the latter from cadmium (Cotzias and Selleck, 1960; Gunn, Gould and Anderson, 1963), and preventing the degree of substitution which could occur in the unprotected ventral prostate. Further, the element when injected into the dorsolateral lobe may diffuse back into the ventral lobe or be recirculated into the ventral lobe. Waites and Setchell (1966) showed a similar pattern of cadmium attraction to the ventral lobe where local vascular changes were marked, the dorsolateral lobe being almost unaffected. The cell fraction and autoradiographic studies show that the cadmium is present in the prostatic parenchyma, in the nuclear and supernatant fractions primarily. Cotzias and Papavasiliou (1964) postulated that zinc is involved in DNA/RNA codes and that the replacement of this zinc by cadmium results in changes within the cell. Further evidence in support of this is presented here by the autoradiographic findings which demonstrate the ^{115m}Cd in the nuclear chromatin. Kar and Chowdhury (1966) showed that the highest intracellular concentration of zinc was in the nuclear fraction, again stressing the pattern of cadmium/zinc substitution within the cell.

The selective affinity of the kidney cortex for cadmium has already been reported (Gunn and Gould, 1957) and is confirmed here. This agrees with other workers who have commented on the nephrotoxicity of cadmium (Kazantzis, 1963; Adams, Harrison and Scott, 1969). The relatively small amounts of cadmium injected did not cause testicular changes. The results show a significant amount of the isotope in the testis but insufficient to cause histological changes.

The positive correlation between prostatic cancer and high ambient cadmium (Potts, 1965; Kipling and Waterhouse, 1967), the substitution of cadmium for zinc (Cotzias, Borg and Selleck, 1961) and the concentration of zinc in human (Daniels *et al.*, 1956) and rat dorsolateral prostate (Gunn *et al.*, 1955) caused the present authors (Scott and Aughey) to suspect a relationship between zinc substitution by cadmium and prostatic cancer. In a histological study (Scott and Aughey) changes were observed in both ventral and dorsolateral lobes of the prostate after a single injection of cadmium, but carcinoma was seen only in the ventral lobe. The results reported here show that some ^{115m}Cd is retained in the prostate over the period of the experiment and provide, at least, suggestive evidence that there is a difference between ventral and dorsolateral prostate in their handling of the available isotope.

Summary

The gonadal effects produced by injection of cadmium in the rats are well known. The effects of direct injection into the prostate are less well understood. The present experiments indicated the retention of cadmium by the various lobes of the rat prostate following direct injection of radioactive cadmium into the organ.

The cells of the prostate are capable of retaining cadmium in measurable amounts up to at least 6 weeks following the injection. The subcellular fractions were measured with respect to cadmium activity and these are indicated. In addition measurements were made in organs which are known to be affected by cadmium, that is, the kidney and the testicle. The affinity of the kidney for cadmium is confirmed.

The areas of the prostate gland with a high zinc content appear to retain less cadmium than areas of the gland which are known to have a low zinc content. This suggests a possible zinc protective mechanism.

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Short Case Report

Primary Hydatid Cyst of Bladder

Hydatid disease can affect any part of the body. In 75% of cases hydatid affects the liver (1st filter) and in 15% the lung (2nd filter). Brain is the 3rd most common site, and less commonly it may involve spleen, muscles, breast, thyroid, parotid and submandibular gland (Talib, 1968). Infestation of the genito-urinary tract is rare, and usually affects the kidney, where the disease may be primary or secondary by involvement from adjacent viscera (Kirkland, 1966). Involvement of the bladder is most infrequent.

Case Report

A 10-year-old male resident of Nepal was admitted with complaint of a lump in the hypogastrium for 6 months. On examination there was a cystic lump in the hypogastrium 16 x 13 cm which was mobile from side to side. The upper limit was well defined, and the lower limit went below the pubic symphysis. On rectal examination the lump was bimanually palpable and was well above the prostate.

Catheterisation did not reduce the size of the lump. Urine examination did not reveal any abnormality. Hb. was 12 gm%. WBC count was 10,600/cu mm, and differential count showed P68, L19, E13, MO. X-ray chest was normal. Plain X-ray abdomen and IVP showed a soft tissue shadow in the lower abdomen Cystogram revealed an extravesical lump which distorted the fundus of the bladder. Cystoscopy was normal. Casoni test was positive.

Exploration was done by a supra-pubic transverse incision. After pushing up the peritoneum the lump was found to be attached to the fundus of the urinary bladder. The cyst was removed intact along with part of the bladder wall (Fig.).

The peritoneum was opened and a search was made for a primary site in the liver, spleen, kidney, gall bladder, stomach, small bowel and large intestine, but all appeared normal. The abdomen was closed around a drain, and the patient made an uneventful recovery.

On section the cyst was found to contain many cysts filled with clear fluid. Microscopically, the primary cyst contained secondary cysts in which were found scolices characteristic of *E. granulosus*.

Comment

Primary hydatid cyst of the urinary bladder is extremely rare, and has its origin after passing through two filters, *i.e.*, liver and lung, via the systemic circulation. Most case reports in the literature are of secondary hydatid cysts. Trevor Lewis (1939) has reported a case from the vesico-prostatic junction which simulated enlargement of the prostate. Constantian and Bolduc (1968) have reported a secondary hydatid cyst of the urinary bladder which had been arising primarily from the mesentery. Talib (1966) has reported a secondary hydatid cyst directly communicating into the bladder from the broad ligament of the uterus, and he even doubted the presence of primary hydatid cyst.

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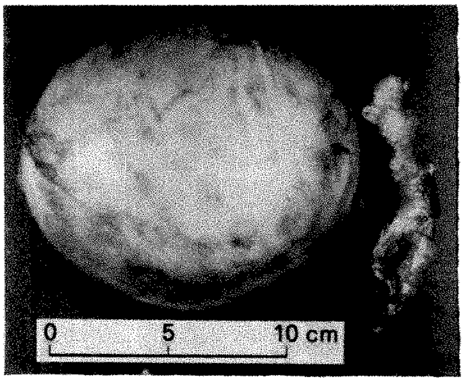

British Journal of Urology (1975), **47**, 193–202

Adrenergic and Cholinergic Receptors in the Human Prostate, Prostatic Capsule and Bladder Neck

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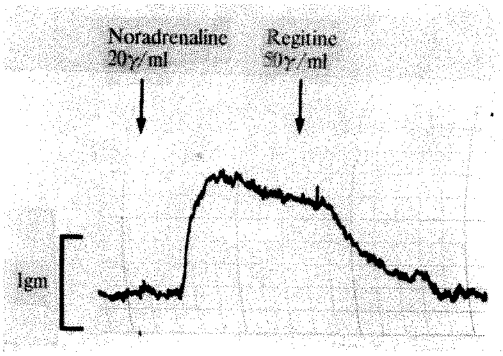
In a recent paper, we have reported the results of an investigation into the pharmacological receptors of the ventral prostate of the rat. In that investigation, we reached the conclusions that the muscular tissue in this gland is rich in α-adrenergic receptors, that β-adrenergic receptors are practically absent, and that cholinergic receptors are present in a moderate degree (Raz, Zeigler and Caine, 1973). As pointed out there, although a great amount of work has been done on the glandular activity of the prostate, very little has been published on the pharmacological reactions of its muscular components. This would seem to be an important omission when one considers that many of the pathological effects of abnormalities of the prostate gland in the human are associated with mechanical disturbances which can, in part at least, be related to its muscular tone, rather than to its glandular activity. With this in mind, the question arises as to what extent our findings in the rat prostate have any counterpart in the human prostate, and hence a possible relationship to clinical disturbances.

The unreliability of simple extrapolation of findings from one species to another, particularly when dealing with pharmacological reactions in tissues, is well recognised. In addition, when trying to relate the findings in the rat prostate to the human prostate, especially in the case of the pathologically enlarged gland, it has to be remembered that the reactions in the human may prove to vary according to whether the surgical capsule of the gland or the adenomatous enlargement is examined. Moreover, if one wishes to complete the picture in relationship to any possible clinical effects on the urine flow, one cannot ignore the possible contribution of the muscle in the bladder neck region. In order to obtain a comprehensive understanding of the pharmacological reactions of this region in the human, it was decided therefore to examine all these structures—the prostatic capsule, the prostatic adenoma, and the bladder neck tissues—in order to determine certain of their pharmacological reactions.

Materials and Methods

The material for a series of in-vitro isometric studies was obtained during the course of operations for benign prostatic enlargement. The operations were performed by the retropubic route, and the first specimen was obtained from the anterior capsule of the prostate. When opening this by a horizontal incision, a second incision parallel and inferior to the first was made, thus providing a transverse strip approximately 2 mm wide by 2 cm long. Care was taken that this contained only capsular tissue, and that it was not exposed to any diathermy or other trauma. The second specimen was obtained from the enucleated prostate itself, a strip of approximately the same size as above being taken transversely from the depths of one of the lobes. A third specimen was taken from the bladder "neck", and in the course of the investigation the nature of this was modified. At first, a transverse strip was taken from the posterior "bladder neck", which is routinely excised in the form of a broad "U"—not a "wedge" (Caine and Pfau, 1963)—during operation. However, the inconsistency of the initial results we obtained, especially with cholinergic



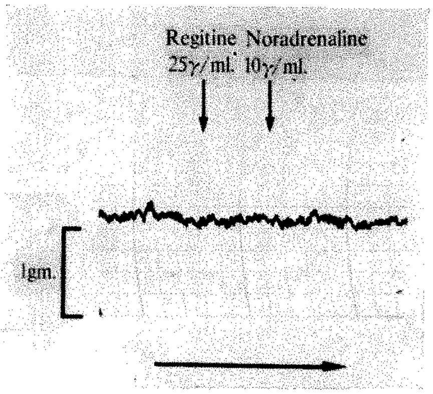
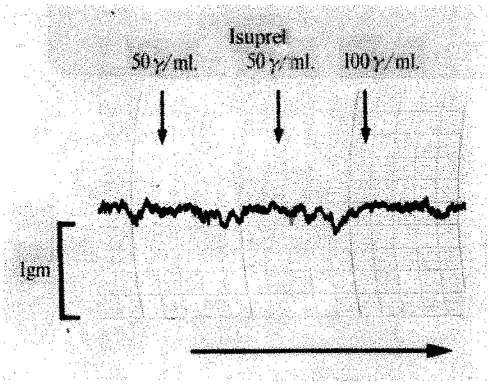


Fig. 1. Response of prostate to α-adrenergic stimulation with noradrenaline, abolished by blockade with Regitine.

Fig. 2. Prior blockade with Regitine prevents response to noradrenaline.



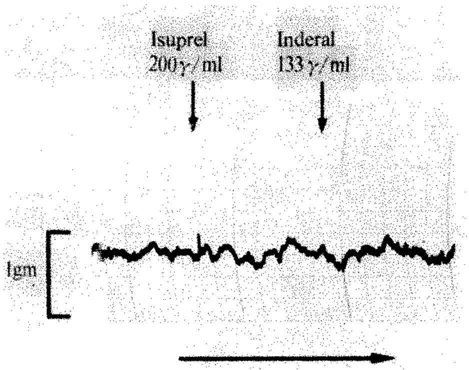


Fig. 3. Lack of response to β-adrenergic stimulation with high concentration of Isuprel.

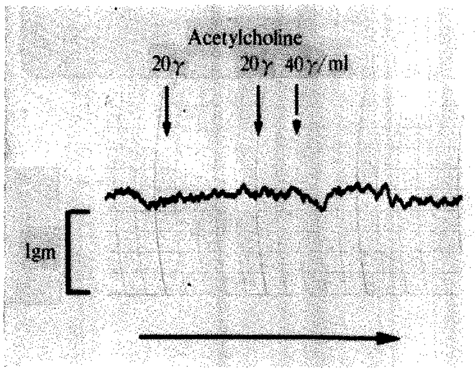
Fig. 4. Lack of response to β-adrenergic stimulation of blockade.

stimulation, led us to modify this specimen; and we subsequently endeavoured to subdivide the strip obtained from the posterior aspect horizontally, into a superficial or trigonal part, and a deep part. In addition, we took an entirely separate specimen from the anterolateral aspect of the bladder neck for comparison. The earlier, simple specimens of posterior bladder neck will be designated as "gross" specimens.

Each specimen was immediately placed in Locke's solution No. 2 at 5°C, and then transferred to Locke's solution No. 2 at 37°C in a muscle chamber, and the isometric responses to adrenergic and cholinergic drugs and blockers studied as described in our previous papers, using a force displacement transducer (Grass FTO3C) and a Grass recording system. A total of 210 experiments were performed on the tissues thus obtained.

Results

After a variable period of up to 1 hour, all specimens were found to exhibit spontaneous muscular activity, characterised by arrhythmic low-amplitude contractions, similar to those seen in the urethra and in the rat prostate. Following the appearance of this activity, the various drugs to be tested were added to the fluid in the muscle chamber. The results of the many experiments performed may be summarised as follows:



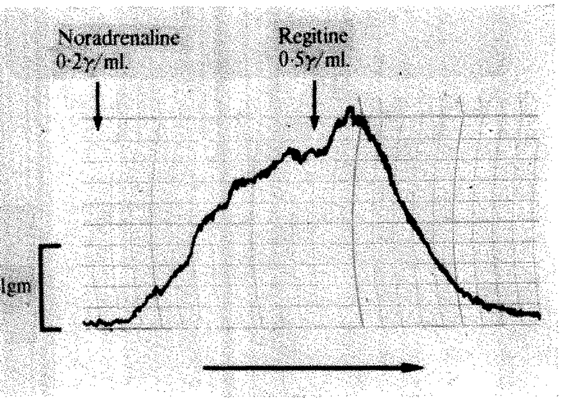


Fig. 5. Lack of cholinergic response of prostate despite high concentration of acetylcholine.

Fig. 6. Marked response of prostatic capsule to α-adrenergic stimulation and blockade. Note low concentration of drugs.

(a) Prostate (Prostatic "Adenoma") (37 experiments)

1. *α-adrenergic agents*

In all cases except one, there was a sharp response to noradrenaline (10 to 20 γ/ml), which was blocked by subsequent or prior addition of Regitine (phentolamine) (25 to 50 γ/ml) (Figs. 1 and 2). The magnitude of the response varied from case to case, and in general was relatively low as compared with the other tissues examined.

2. *β-adrenergic agents*

There was no response to Isuprel (isoproterenol) (<200 γ/cc) or to Inderal (propranolol) (<133 γ/ml), even in the very high concentrations indicated (Figs. 3 and 4).

3. *Cholinergic agents*

There was no response to acetylcholine, even in concentrations as high as 80 γ/ml (Fig. 5).

(b) Prostatic Capsule (56 experiments)

1. *α-adrenergic agents*

In all cases except one, there was a sharp and pronounced response to noradrenaline, which was blocked by Regitine. In some cases there was extreme sensitivity to even very small concentrations of the noradrenaline, *e.g.*, 0·2 γ/ml (Fig. 6), and in general, the magnitude of the response was greater than that of the prostate itself.

2. *β-adrenergic agents*

The results obtained were variable. In 12 out of 19 experiments, there was no response, even when very high concentrations were used (*e.g.*, Isuprel 300γ/ml) (Fig. 7). In 6 cases there appeared to be a mild or moderate effect, but the fact that in 5 of these there was no reversal of the apparent effect by Inderal makes it questionable whether these were indeed true beta responses (Fig. 8). In 1 case there was a *fall* in tension in response to Inderal, *i.e.*, a reversal of the normally expected beta blocking effect.

3. *Cholinergic agents*

There was a marked response to acetylcholine in low concentrations (0·25 to 2 γ/ml), which was blocked by atropine (Fig. 9). Only 1 case out of 15 failed to react.

(c) Bladder Neck—"Gross" (28 experiments)

1. *α-adrenergic agents*

In all cases there was a good response to noradrenaline, which was blocked by Regitine. It was notable that this contraction appeared to be relatively slow in developing, resulting in a "climb-

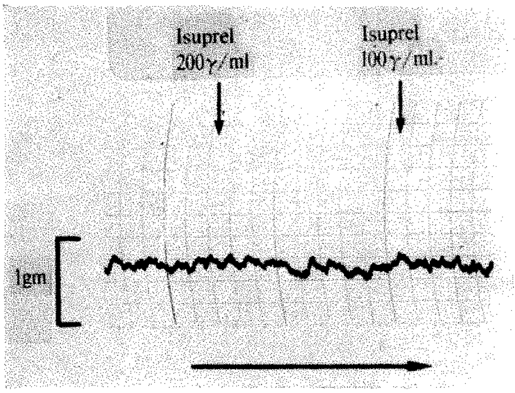
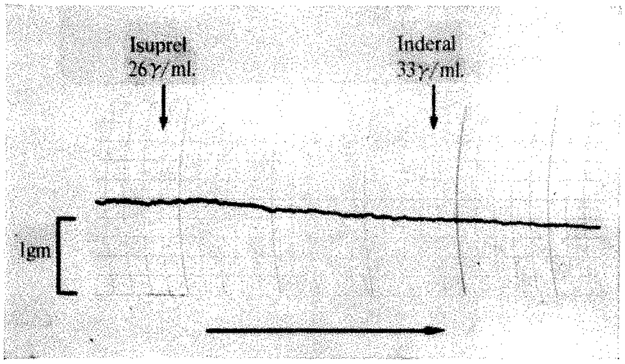


Fig. 7. Lack of response of capsule to very high concentrations of Isuprel.



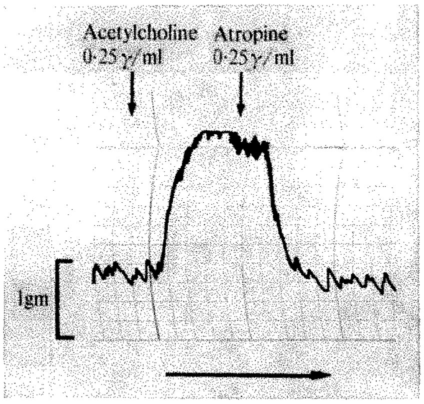


Fig. 8. Apparent response of capsule to β-adrenergic stimulation with Isuprel, but no blocking effect by subsequent addition of Inderal.

Fig. 9. Marked response of capsule to cholinergic stimulation with low concentration of acetylcholine, abolished by subsequent administration of atropine.

ing" curve, as compared with the generally abrupt response of the other tissues to α-adrenergic stimulation (Fig. 10).

2. *β-adrenergic agents*

No response was obtained in 11 out of 12 experiments. In the remaining 1, there appeared to be a reversal of the normal effect of Isuprel, with a slight increase in tension.

3. *Cholinergic agents*

In 5 out of 8 experiments there was a slight to moderate response to acetylcholine, which was blocked by atropine. In the other 3, there was no response.

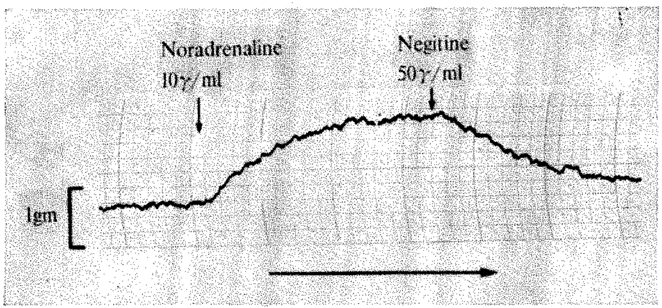
(d) Bladder Neck—"Superficial" (26 experiments)

1. *α-adrenergic agents*

In 9 out of 10 cases, there was a good response. This was in the same order of magnitude as in the "gross" bladder neck specimens, and once again the tendency to a relatively slow contraction was discernible.

2. *β-adrenergic agents*

In 7 out of 8 cases there was no response at all. In one case there was a slight fall in tension following Isuprel (26 γ/ml), but this was not affected by subsequent Inderal (30 γ/ml), and may therefore not have represented a true beta response.



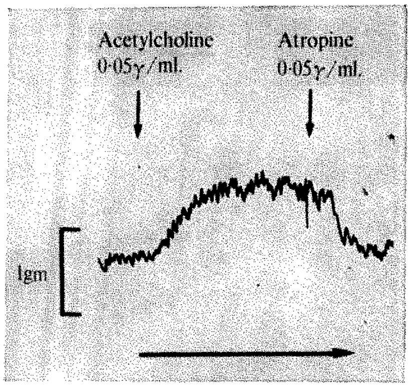


Fig. 10. Response of "gross" bladder neck specimen to α-adrenergic stimulation with nordarenaline, blocked by Regitine. Note relatively slow development of contraction.

Fig. 11. Cholinergic response of tissue from "deep" bladder neck. Note very low concentration of acetylcholine used.

3. *Cholinergic agents*
There was a slight to moderate response in 5 out of 8 cases. In the other 3 there was no response.

(e) Bladder Neck—"Deep" (36 experiments)

1. *α-adrenergic agents*
In 9 out of 14 cases there was a slight to moderate alpha response. In the other 5, there was no response.

2. *β-adrenergic agents*
There was no response at all, or an equivocal one, in 8 out of 9 cases. In the remaining one there was a definite fall in tension in response to 26 γ/ml of Isuprel, but this was not blocked by 20 γ/ml of Inderal.

3. *Cholinergic agents*
4 out of 13 specimens failed to show a response to acetylcholine. The other 9 showed a response which varied from mild to very marked (*e.g.*, a sharp response to as little as 0·05 γ/ml of acetylcholine, abolished by the same concentration of atropine (Fig. 11).

(f) Bladder Neck—"Antero-lateral" (27 experiments)

1. *α-adrenergic agents*
5 out of 9 specimens showed an α-adrenergic response, and the other 4 showed no response. When present, the rise in tension was relatively gradual.

2. *β-adrenergic agents*
This was uniformly negative in all 8 specimens examined.

3. *Cholinergic agents*
There was a good cholinergic response in 9 of the 10 specimens tested. The magnitude of the response varied, in some cases being relatively great.

Discussion

In recent years there has been an increased interest in the pharmacological reactions of the smooth muscle of the urinary tract, and in particular in the part played by the adrenergic receptors in this tissue. We ourselves have demonstrated the presence of both α and β receptors in the urethra (Raz and Caine, 1972 Raz, Zeigler and Caine, 1972), and others have reported on the presence and distribution of these receptors in the urinary bladder (Edvardsen and Setekleiv, 1968). The close association of the prostate with the urethra, both anatomically and embryologically, and the relatively large amount of smooth muscle tissue therein, suggested that similar receptors might be present in the prostate, and if found might have some functional significance not only in relation to the sexual activity of the gland, but also in relation to the act of micturition. The report by Owman and Sjöstrand (1965) of their demonstration, by fluorescent microscopic techniques, of short adrenergic neurones supplying the muscular tissue of mammalian prostate glands has been supplemented by Baumgarten *et al.* (1968), who have similarly demonstrated these neurones in human prostatic tissue removed at operation, and have shown that the bulk of these innervate the smooth muscle fibres. These anatomical findings would lead one to expect a sympathetic response in the prostate, and we have already demonstrated this in a dynamic fashion in the rat prostate, as mentioned above.

In investigating this matter in the human prostate, it seemed desirable to investigate separately the clearly defined parts of the prostate encountered at operation, namely the "hyperplastic" or "adenomatous" part which is enucleated, and the enveloping capsule. It is clear from our results that there is a marked difference in the response of these two tissues. In both tissues there was a definite response to α-adrenergic stimulation, but the magnitude of this response was generally much greater in the capsule than in the "adenoma". (It seems reasonable to discount the 1 odd case in each group which did not react, as being a technical failure, in view of the uniformity of the results in the other specimens.) This marked difference in the strength of the reaction of the capsule as compared with that of the hyperplastic prostate may to some extent be explained by the difference in the relative amount of muscular tissue in each of them, as described by Hunter (1968). However, it may also represent a true difference in the degree of sensitivity of the muscle tissue itself, in view of the other differences discussed below.

The responses to β-adrenergic stimulation also appear to be different. In the hyperplastic prostate there was no evidence of any response at all. In the capsule there was similarly no response in about 60% of specimens, but a questionable response was obtained in the remaining specimens.

In view of the obvious importance of the cholinergic supply to the muscle tissue in this region, it was decided to extend the investigation to include the effect of acetylcholine, coupled with the blocking effect of atropine. Some animal experiments in the past had indicated that the prostatic muscle is devoid of parasympathetic receptors (Macht, 1922), whereas in our own rat experiments referred to above, we obtained a moderate parasympathetic response. However, it is noteworthy that in these experiments we examined the whole ventral prostate, including the capsule, and no differentiation was possible between the responses of the capsule and the prostatic muscle proper. It was in fact, in this response that the greatest difference between the two components of the human prostate was seen. Whereas the "adenoma" was completely unresponsive to cholinergic stimulation, the prostatic capsule showed a marked response with high sensitivity in virtually every case. This very clear and definite difference can not be explained in this instance simply by differences in the proportion of muscle in the two tissues, but must represent a qualitative difference in the type of muscle, the one being rich in cholinergic receptors and the other lacking them. This would be difficult to account for according to the usually accepted description, namely that the surgical capsule of the prostate consists essentially of compressed normal prostatic tissue. However, it would accord well with the thesis put forward by Hutch and Rambo (1970), namely that the muscle in the capsule is not derived from the prostate, but is entirely distinct and represents the outer circular muscle layer of the urethra.

When one comes to consider the "bladder neck" region, the different responses obtained are interesting and instructive. It was felt that the relatively poor or absent cholinergic response of the tissue removed from the posterior "bladder neck" in the early group of "gross" specimens indicated that the muscle being examined was probably predominantly from the superficial and

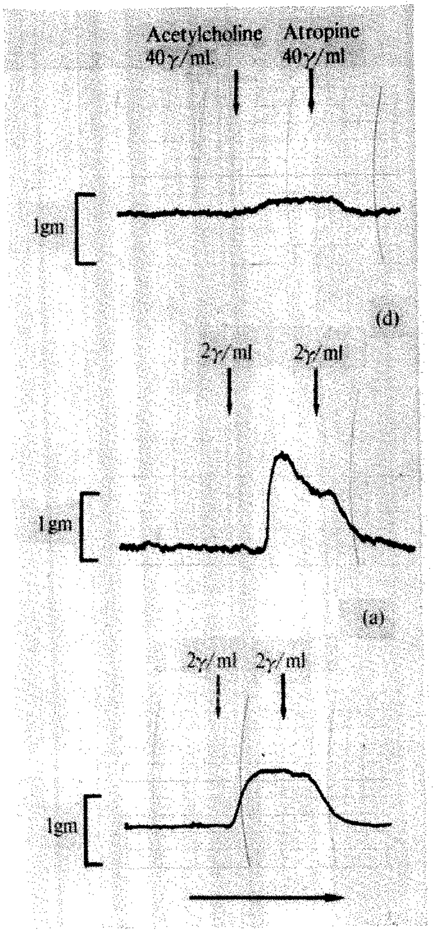


Fig. 12. Comparative responses of superficial (s), deep (d) and antero-lateral (a) specimens of bladder neck muscle to cholinergic stimulation and blockade, in same patient. Note that 20-fold concentration of drugs is used in superficial specimen.

deep layers of the trigone, with only minor contributions from the detrusor muscle (Tanagho and Smith, 1966). A comparable finding in dogs was reported by Rohner and his colleagues (1971). They noted that whereas strips of detrusor muscle responded consistently to cholinergic stimulation, this response was absent in strips taken from the trigone and postero-lateral bladder neck. Specimens taken from the anterior bladder neck showed a similar, but less marked response to that of the detrusor. The trigonal layers, being of mesodermal origin, would be primarily sympathetic in their response, whereas the detrusor, which is endodermal in origin would be rich in cholinergic receptors (Tanagho *et al.*, 1966). In an attempt to verify this supposition and define the component parts of the excised specimen more precisely, an attempt was made in the later cases to divide the specimen obtained into two layers, as described in the introduction. By doing this, it was felt that the more superficial part should be predominantly trigonal muscle, whereas the deep part should contain a greater proportion of the true detrusor muscle in the bladder neck region. The subdivision could only be made roughly, at operation, and it was clear that pure specimens, especially of the deeper layer, would not be obtained, especially as the thickness of this posterior lip and of the specimen excised inevitably varied from patient to patient. At the same time, in order to provide comparative tissue from the bladder neck region

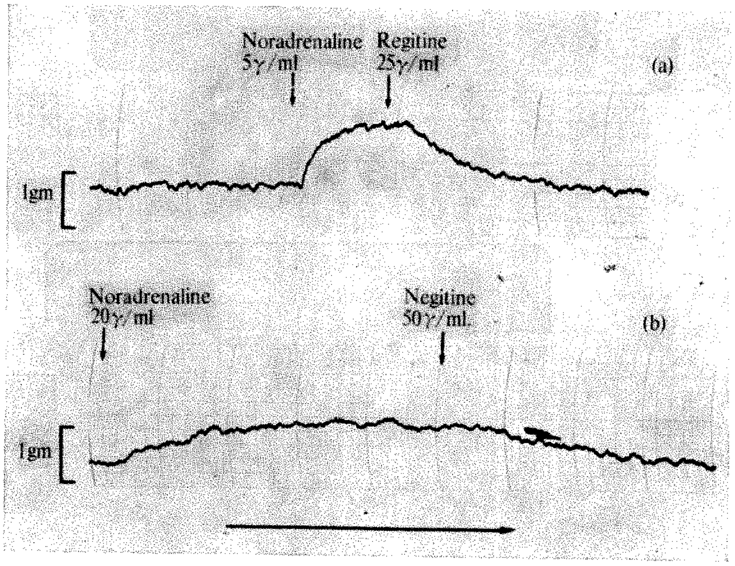


Fig. 13. Comparison of muscle response to α-adrenergic stimulation in capsule and in bladder neck. Latter is much more gradual in nature.

which would be completely clear of the trigonal muscle, the additional specimens were taken from the antero-lateral aspect of the bladder neck.

The results of the tests carried out on these various specimens may be said, in general, to support the impression that what one is excising posteriorly at operation, and loosely refers to as the "posterior bladder neck", is in fact, predominantly trigonal muscle. Thus, when comparing the responses of the various tissues in the same patient, one finds that the cholinergic response is always very poor in the superficial as compared with a good response in the deep and/or antero-lateral specimens (Fig. 12). One receives the impression, in fact, that such poor response as is obtained in the superficial specimens may well be due to the inclusion of some deep muscle fibres, and that the trigonal muscle itself is probably completely lacking in cholinergic receptors. The α-adrenergic response of these tissues was variable, sometimes the superficial tissue being better, sometimes the deep. However, in general, an α-adrenergic response was obtained, as would be expected from the observations on the sympathetic response of the bladder neck by Kleeman (1970) and others. One characteristic that was noted in these α-adrenergic responses was that the contraction of the muscle was relatively slow in nature, as compared with the much more abrupt and active response of the capsule and the prostate itself (Fig. 13). This may reflect a difference in the normal functional activity of the different tissues, the bladder neck and trigonal muscle producing a more gradual, sustained rise in tone appropriate to closure of the bladder neck, whereas the prostatic tissue requires a more decisive reaction to stimulation, as in ejaculation. For all practical purposes, the β-adrenergic response in all bladder neck specimens, if present at all, was so weak as to be of no significance.

The conclusions reached above may possibly be not only of academic interest, but could also have certain clinical implications. As a result of our earlier observations on the α-adrenergic receptors in the rat prostate, we postulated that if similar α-adrenergic receptor activity were to be found in the human, there may lie therein an explanation for certain cases of acute retention of urine in the presence of benign prostatic enlargement. Every urologist is familiar with the patient who presents with a sudden acute retention of urine due to an enlarged prostate, and yet prior to the acute episode has had minimal symptoms, or even denies any symptoms at all. Moreover, following relief of the acute retention, a proportion of these patients will start passing urine satisfactorily once again, and may never have any further attacks (Chapman, 1949). The medical literature is remarkably silent regarding the mechanism of such sudden attacks of acute retention. The explanation of sudden "congestion" of the prostate is frequently mentioned, but no clear information as to the nature of this is forthcoming. Sudden infarction in the prostate may sometimes furnish an explanation, but although areas of infarction are occasionally seen in the removed specimens, this cannot account for the majority of cases, nor is it likely to be a satisfactory explanation in the transitory cases. Acute inflammation in the enlarged prostate may explain an occasional case, but in the absence of concomitant evidence of acute prostatitis or prostatic abscess is unlikely to be the explanation in more than rare instances.

Certain circumstances have been recognised by clinicians as being liable to provoke an attack of acute urinary retention in the prostatic patient. One of these is over-filling of the bladder due to inability to void for social or other reasons, or due to the effect of a diuretic. Another is the taking of medicines containing sympathomimetic drugs, such as a cough medicine containing ephedrine, and a further precipitating cause may be chilling of the body. It is noteworthy that all these precipitating factors are characterised by a common feature, namely, an increase in sympathetic activity. The increased sympathetic activity produced by bladder filling is well known in its unbalanced, excessive form as seen in the case of the high paraplegic patient (Cunningham *et al.*, 1953). However, it is perhaps not so widely realised that a similar, though more balanced, sympathetic reaction to overdistension of the bladder occurs also in the normal individual (Taylor, 1963). Chilling of the body is well known to result in increased sympathetic activity (Keele and Neil, 1971), and the administration of sympathomimetic drugs such as ephedrine is self-evident. In view of the presence of α-adrenergic receptors in all the tissues we have examined in the present investigation, and in particular the very great sensitivity in certain cases, of the prostatic capsule, it seems reasonable to conclude that increased sympathetic activity in a patient with an enlarged prostate may, in some cases at least, result in a sudden increase in tension in the prostate, and particularly in the prostatic capsule. This in turn will produce a corresponding increase in the intraurethral closure pressure in an already partly obstructed urethra, and can throw the patient into sudden acute retention. It should be emphasised that it is not suggested that all instances of acute retention of urine in the prostatic patient are due to this cause, but it does seem probable that many cases of retention of the type described are due to over-stimulation of the α-adrenergic receptors, particularly in the prostatic capsule, with "clamping down" on the prostatic urethra.

Our demonstration of the marked cholinergic response of the prostatic capsule, also has a clinical implication, in that it furnishes pharmacological support for a known clinical fact. Cholinergic drugs are frequently used to increase the expulsive force of the bladder detrusor, and even to induce micturition in certain cases of urinary retention. However, it is generally accepted that the use of such drugs is not indicated in the treatment of retention due to an enlarged prostate. This is now seen to be logical, for it is evident from our findings that any increase in tone of the detrusor produced by cholinergic drugs is liable to be counteracted by a simultaneous increase in tone of the prostatic capsule, compressing the prostatic adenoma and the enclosed urethra, and hence increasing the degree of urinary obstruction. Thus, although in the absence of an enlarged prostate cholinergic drugs may successfully be used, they should be regarded as contraindicated in its presence.

Summary

The adrenergic and cholinergic receptors of the human prostatic capsule, prostatic "adenoma", and bladder neck, were investigated by the in-vitro isometric technique.

The prostatic capsule was found to be very rich in both α-adrenergic receptors and cholinergic receptors. The prostatic adenoma was moderately rich in α-adrenergic receptors, but cholinergic receptors were absent. β-adrenergic receptors were absent in the prostatic adenoma, and there was an equivocal response in less than half the specimens of the prostatic capsule.

An attempt was made to distinguish between the trigonal component at the posterior bladder neck, and the true bladder neck muscle both posteriorly and antero-laterally. The results indicate that the "posterior bladder neck" seen at operation is predominantly trigonal muscle, and is poor in cholinergic receptors. The adrenergic response is variable in the true bladder neck muscle, but is present and strong in the trigonal muscle. This response is characteristically gradual in its development.

In view of the findings in this investigation, it is suggested that certain instances of acute retention of urine in prostatic patients are due to over-stimulation of the α-adrenergic receptors, particularly those in the prostatic capsule. Similarly, the accepted clinical contraindication to the use of cholinergic drugs for retention in the prostatic patient is supported by the distribution of the cholinergic receptors in the tissues examined.

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The Effect of Dicynene on Blood Loss during and after Transurethral Resection of the Prostate

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Bleeding is the major complication of prostatectomy however it is done. Profuse bleeding increases the operating time, the need for irrigation and the duration of the indwelling urinary catheter, factors, especially the last, which play an important role in causing and maintaining postoperative urinary infection (Symes *et al.*, 1972).

The anaesthetic may influence blood loss during the operation, but has little effect afterwards. There is conflicting evidence about the value of spinal anaesthesia (Slade *et al.*, 1964; Madsen and Madsen, 1967): and the value of hypothermia, or cooling the irrigation fluid is not established (Madsen, Kaveggia and Atassi, 1964; Robson and Sales, 1966). Bruce, Zoras and Still (1960) observed a 50% reduction in pre- and postoperative blood loss with controlled hypotension but this carries a risk of cerebral and myocardial infarction in elderly men (Madsen and Madsen, 1967).

Many drugs have been tried to reduce postprostatectomy haemorrhage but none has been of any use: *e.g.*, carbazochrome salicylate (Frank and Lloyd, 1959), Kutapressin (Weisenthal *et al.*, 1961), Premarin (Madsen *et al.*, 1964), polyoestradiol phosphate (Madsen *et al.*, 1968) and aprotinin (Pearson, 1969). Only epsilon aminocaproic acid (Lawrence, Ward, McQuaid and Holdom, 1966; Madsen and Strauch, 1966; Vinnicombe and Shuttleworth, 1966) has been found to reduce *post*operative blood loss by 30% to 60% but it has no effect on bleeding during operation.

Diethylammonium 1, 4-dihydroxy-3-benzone sulphate (dicynone, Dicynene) was introduced in 1959 by Regne and Laporte. Animal experiments and clinical trials in patients suggested that it increased platelet adhesiveness, the rate of release of intrinsic thromboplastin and the capillary resistance, and reduced the bleeding time.

The increased platelet adhesiveness did not apparently increase the incidence of deep venous thrombosis (Negus, Pinto and Brown, 1969).

Clinical reports have been very favourable in vascular and middle ear surgery, and in surgery of the buccal cavity (Arias, 1966; Guerrier, 1966; Held, 1966). We therefore decided to set up a double blind trial to measure the effect of Dicynene on pre- and postoperative bleeding after transurethral resection of the prostate.

Patients and Methods

Series

87 patients entered the trial, each had a clinical diagnosis of benign enlargement of the prostate and was considered suitable for transurethral resection. Subsequently 11 of these patients were found to have carcinoma in the tissue removed at operation and were excluded from this study.

Before operation pulse rate, blood pressure, drugs likely to affect haemostasis, haemoglobin, platelet count, blood urea and euglobulin lysis time were all measured. The technique of preparation and operation has been described (Symes *et al.*, 1972).

Anaesthesia

Patients were premedicated with intramuscular pethidine and promethazone hydrochloride, induced with thiopentone, and maintained with nitrous oxide, oxygen and methoxyflurone. When the patient was settled a caudal epidural block was induced with 0·5% bupercaine with adrenaline. All the operations were done by the same surgeon (J. P. B.), ignorant of the drug being given.

Treatment was allocated to the first 46 patients on a single blind basis, in alternating blocks of 10. The last 41 patients were allocated treatments double blind and in random order.

The *treated* group were given 1 g Dicynene intravenously in the anaesthetic room. In the postoperative period 250 mg were injected intramuscularly at 4 hourly intervals until macroscopic haematuria had ceased. The *placebo* group were given equal volume injections of normal saline according to a similar schedule.

Bladder washings at operation were collected in a graduated water bath. The blood loss was estimated colorimetrically by the acid haematin method (Sahli, 1931). In the postoperative period all the bladder washings were collected and the haemoglobin content of each 10 litre sample was measured until macroscopic haematuria had ceased.

Deep Vein Thrombosis

The incidence of deep vein thrombosis was studied in 16 of the patients given Dicynene, using ^{125}I-fibrinogen. A Pitman Isotope Localisation Counter Model 235 was used to count the medial surface of each thigh and calf at 10 cm intervals with the legs elevated to 15° to obviate venous pooling (Atkins and Hawkins, 1965). The criteria for the diagnosis of deep vein thrombosis were those of Negus *et al.* (1968).

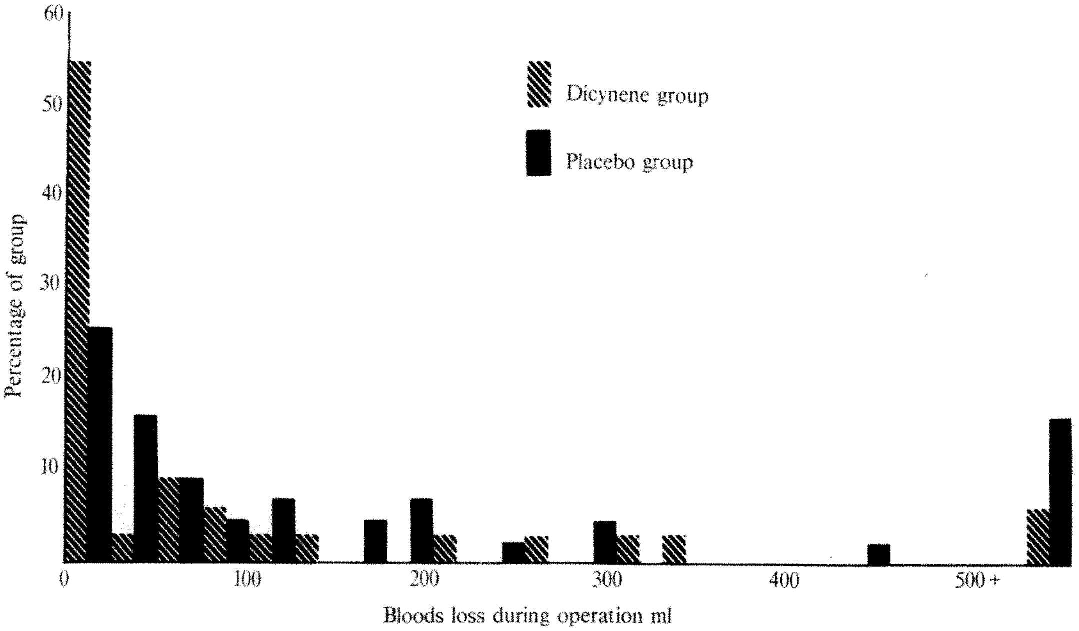

Fig. 1. Blood loss during operation in placebo and Dicynene treated groups. Median blood loss in placebo group = 72 ml, median blood loss in Dicynene group = 17 ml (p = 0·001, Mann Whitney U-test, 2 tailed).

Statistical Methods

The effects of treatment were compared using t-tests when the variables were normally distributed, and Mann-Whitney U-tests when they were not.

Results

Since the distribution of many of the variables we measured was highly skewed (Fig. 1) we used the median value in preference to the mean (Table). Retrospective examination of the 2 treatment groups shows that they were well matched with respect to age, blood pressure, blood urea, euglobin clot lysis times and platelet counts.

When the effects of treatment on the first 46 patients to be admitted to the trial were compared with the last 41, no change in trend could be detected. It was concluded that the single blind allocation of treatments to the first group was unlikely to have been biased, and that further analysis could be carried out regarding the patients as a single group.

Median loss of blood at operation in the Dicynene group was 17 ml compared with 72 ml in the controls ($p<0{\cdot}001$). Postoperative blood loss was also lower in the patients treated with Dicynene (38 ml) than those in the control group (103 ml) ($p = 0{\cdot}05$).

The median weight of tissue resected in the Dicynene group was 5 g and in the placebo group 9 g, but this had no effect on the significance of results even if the blood loss was expressed as ml/g of prostate resected.

In this series although we could find no clinical evidence of deep vein thrombosis, 2 of the 16 patients scanned with ^{125}I labelled fibrinogen showed clear evidence of calf thrombosis. A far larger series would be needed to reveal any extra hazard due to Dicynene.

Discussion

The Dicynene and control groups were well matched with respect to variables which might have affected blood loss: the anaesthetic was uniform, and the operation time was not significantly

Table

Comparison of the Dicynene and Placebo treated groups. Figures in italics refer to the median value of a variable which was not normally distributed. Mean values are given in bold type

	Dicynene (mean or median)	*Placebo* (mean or median)	*Significance*
Number	33	43	—
Age (Yrs)	65	64·8	n.s.
Systolic B.P. (mm Hg)	153	154	n.s.
Diastolic B.P. (mm Hg)	89	89	n.s.
Blood urea	39	37	n.s.
Weight of prostate removed (g)	**5**	**9**	n.s.
Blood loss during operation (ml)	**17**	**72**	0·001
Blood loss during operation (ml/g prostate)	**4·8**	**9·0**	0·001
Blood loss after operation (ml)	**38**	**103**	0·05
Blood loss after operation (ml/g prostate)	**6·3**	**12·0**	0·07
Operation time (min)	**18**	**20**	n.s.

different in the two groups, so it seems likely that the lesser preoperative blood loss in the Dicynene group could be attributed to the drug, and even if the blood loss is expressed as a function of the weight of prostate removed, the significance of these results is the same.

Blood loss during transurethral resection is seldom enough to warrant a blood transfusion, but any reduction in bleeding helps the surgeon to get a clearer view of the field. In this series the mean resection time 18 minutes in the treated group and 20 minutes in the placebo group suggests that any reduction in the preoperative blood loss made little difference.

Prolonged bleeding after the operation is a very different matter: the more the bleeding, the more the irrigation and the longer the catheter drainage, and both are directly related to postoperative infection. Reduction in the postoperative bleeding time should reduce postoperative infection.

Replacement of blood is necessary only if a patient has lost more than 500 ml of blood. This occurred in 9 of our patients; 7 in the placebo group and 2 in the treated group. Postoperative bleeding—sufficiently severe as to require returning the patient to theatre—occurred in 1 patient who had been given Dicynene.

This trial shows that Dicynene reduces blood loss during transurethral resection and may also reduce the postoperative blood loss. It is the first drug described that reduces the bleeding at the operation.

Summary

The effect of Dicynene on blood loss during and after transurethral resection for benign enlargement of the prostate was studied in 76 patients.

Median loss of blood at operation was 17 ml in those given Dicynene compared with 72 ml in the placebo group ($p = <0{\cdot}001$).

Median postoperative blood loss was 38 ml in the Dicynene group, and 103 ml in the placebo group ($p = 0{\cdot}05$).

Clinical evidence of deep vein thrombosis was found in neither group.

Dicynene helps to reduce blood loss in transurethral resection.

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Malignant Mesothelioma of the Testicular Tunica Vaginalis

A 60-year-old man was admitted for hydrocoelectomy because of a swelling of the left side of the scrotum which had been present for 1 year. The swelling was non-tender, positive to trans-illumination and measured 7×4 cm; physical examination showed no abnormality elsewhere. Haemogram, blood chemistry, chest X-ray and I.V. pyelography were all within normal limits. At operation the testis and epididymis appeared normal. The surface of the tunica vaginalis was covered with reddish vegetations and material sent for pathological examination proved to be malignant. A left orchioepididymectomy was performed.

On pathological examination the tunica vaginalis was 1·3 cm thick. Its surface was irregular and consisted of a tumour mass of solid and papillary structures projecting into the space between it and the tunica albuginea. Microscopically the tumour was mainly papillary and occasionally solid and alveolar; it occupied the tunica vaginalis space and invaded the connective tissue underlying the mesothelium (Fig. 1). Its cells had an eosinophilic cytoplasm, sometimes vacuolar, with a large nucleus; there were occasional mitoses and atypia of nuclei. Malignant mesothelioma arising from the tunica vaginalis was diagnosed.

Two weeks later bilateral lower-limb lymphangiography showed filling defects in several enlarged para-aortic lymph nodes at vertebrae L2-3. Laparotomy revealed enlarged glands at the level of L1-3. Pathological examination of a removed lymph node disclosed metastasis of the tumour (Fig. 2). The patient was referred for radiotherapy, and a total of 5,000 rads was given to inguinal, para-aortic, mediastinal and left supraclavicular regions. Follow-up examination 1 year later showed the patient to be in good health. Chest X-rays and a bone survey as well as a liver scan have all been normal.

Comment

Papillary tumours, either diffuse or localised, may arise from the surface of the serous membrane of the tunica vaginalis (Kasdon, 1969). Although uncommon, about 15% are malignant (Campbell, 1963).

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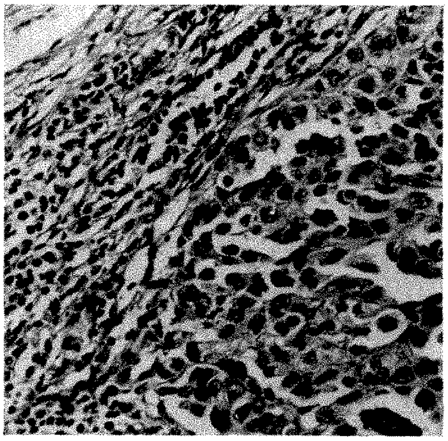

Fig. 1

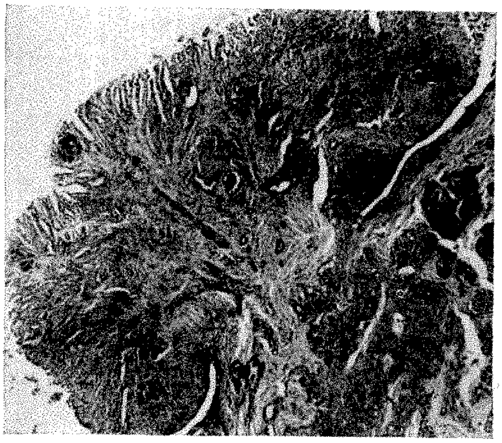

Fig. 2

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Peyronie's Disease

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Although the condition was first remarked upon in an old French 17th century periodical "Les Éphémérides des Animaux de la Nature" (Merle, 1899; Fogh-Andersen, 1957) priority of a detailed study is attributed to François de la Peyronie (1743). The paper he read before the "Académie Royale de Chirurgie" was a classic both in the excellence of presentation of the clinical features and in establishing the benign character of the disease.

Publications concerning various facets of this singular and interesting disease are increasing every year and cases have been reported from nearly every country of the globe.

Although there are certain points still in dispute as a result of clinical observation and study of the pathology, a more precise conception of what the disease implies has now been reached. Aetiology remains the most obscure and most discussed problem.

The purpose of this paper is to present an analysis of a personal series of 250 patients; to submit a report on the effects of a cytostatic drug—procarbazine (Natulan)—on the course of the disease: and to review the literature briefly.

Personal Series

Table I shows the age groups in this series and Table II the duration of symptoms.

Eight of the patients were diabetics.

Table I

Age Groups

19 years	1
20-29 years	17
30-39 years	29
40-49 years	75
50-59 years	102
60-69 years	26

Table II

Duration of Symptoms

Less than 6 months	116
6/12-11/12	52
12/12-17/12	31
18/12-23/12	13
24/12-35/12	7
36/12-47/12	7
4 years	3
5 years	1
6 years	3
Not known	7

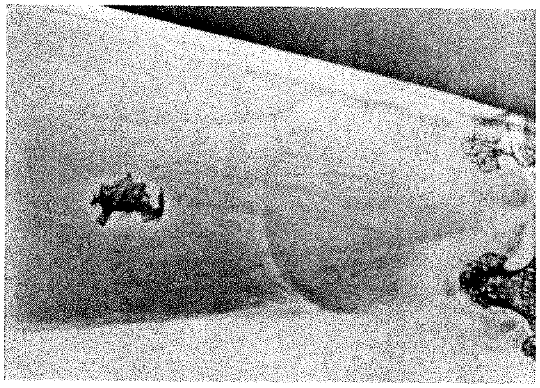

Fig. 1. Penis: Xeroradiography shows a 1 cm plaque of ossification in the penis.

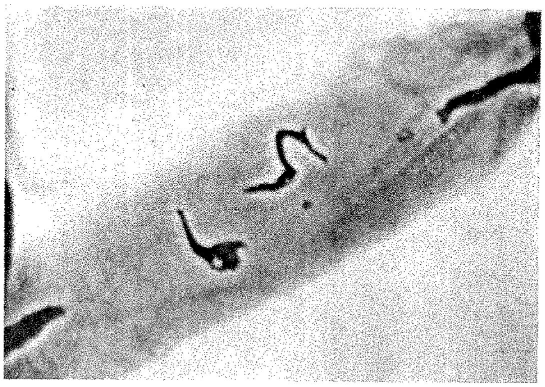

Fig. 2. Penis: Xeroradiography shows four plaques in the septum. Proximal plaque dense and extensive.

Table III

Total Number of Patients = 250

Plaques			
Number of Patients with 1 Plaque	Number of Patients with 2 Plaques	Number of Patients with 3 Plaques	Number of Patients with 4 Plaques
195	51	3	1
Calcification			
Number of Patients with calcification	Number of Patients with calcification	Number of Patients not known	
183	33	34	

Previous Trauma. Five patients in this series sustained injuries whilst the organ was in the flaccid state and Peyronie's disease could have been the predisposing factor. In 4 patients injury occurred during violent attempts at coitus or as "faux pas du coit" with hyperflexion of the rigid penis. The immediate symptoms were severe pain, oedema and an extensive haematoma caused probably by rupture of the tunica albuginea. Calcified plaques were subsequently seen on X-ray films in 2 of these patients.

Table III records the number of plaques without and with calcification in cases of typical Peyronie's disease.

The plaques in the septum and tunica albuginea do not always remain stationary. The proximal plaque sometimes begins to thicken and the posterior border looses itself under the symphysis, whilst the anterior border becomes softer and thinner with treatment.

It is, therefore, often helpful to assess the clinical picture in conjunction with the appearances on X-ray. Xeroradiography (Fig. 1 and 2) possesses advantages over conventional X-ray techniques because it considerably enhances contrast between areas in which there is little difference in density.

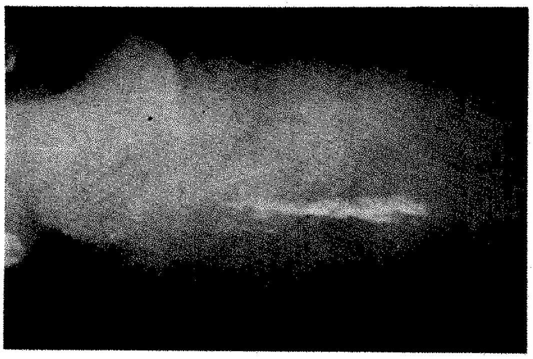

Fig. 3. X-ray penis: extensive calcification of the plaque in the septum (see also Fig. 4).

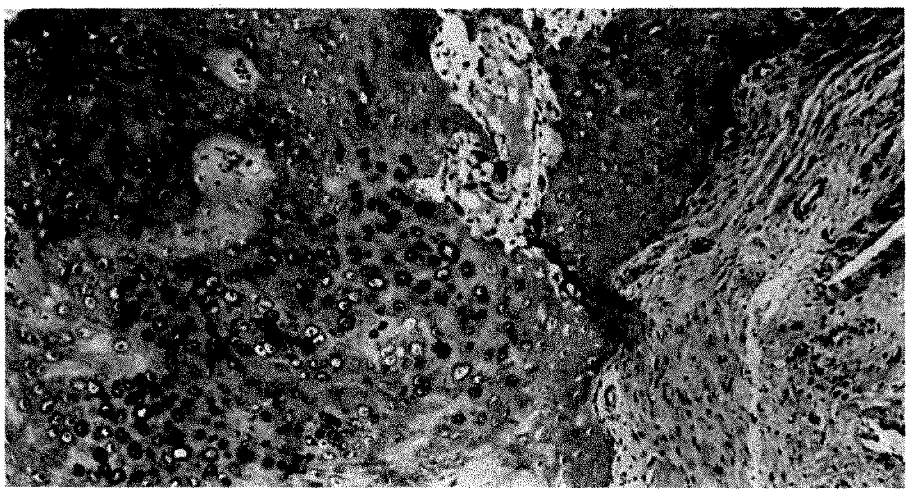

Fig. 4. Excised plaque: photomicrograph of the lesion showing left to right: young (woven) bone, cartilage, young fibrous tissue. Top: marrow spaces and right-young "woven" bone ×-125.

Histological Findings. In 5 patients in the series, corrective operation of the deformity was carried out, providing material for histological examination.

Bone, bone marrow and cartilage were found in 4 of the plaques (Figs. 3 and 4). Normal values were obtained for plasma, calcium and plasma phosphorus in all 5. Other laboratory investigations included estimations of plasma testosterone levels in a few of the patients. The values obtained ranged between 430 ng/100 ml and 740 ng/100 ml with one exception, at 270 ng/100 ml (Normal range 200 to 1200 ng/100 ml).

In recent years the concept that an autoimmune reaction may be the basis of a number of connective tissue diseases has been gaining ground. Table IV shows the number of cases with other fibrotic disorders in this series. Doniach (1971) tested the sera of 10 cases prior to treatment on rat liver substrate for various reactions to connective tissue with negative findings.

Table V indicates various methods of therapy adopted in this series and some of the results that were obtained. The first 5 methods have been in general use, the others were used in the past and later abandoned.

Table IV

Fibrotic Conditions Associated with Peyronie's Disease

	Number of Patients
Subcutaneous fibromata	3
Dupuytren's contracture	8
Bilateral Dupuytren's contracture and plantar fibromatosis	2
A collagen triad. Peyronie's disease, Dupuytren's contracture and fibrosis of the auricular cartilage	2

Table V

Methods of Therapy

	Total	Good Result	Partial Improvement	Not Improved	Not Known
Local corticosteroid injections	23	15	4	2	2
Local corticosteroid injections and Vitamin E	47	26	11	5	5
Local corticosteroid injections, oral prednisolone and Vitamin E	16	9	6	1	...
Prednisolone tablets and Vitamin E	28	9	10	3	6 (1 transfer)
Vitamin E tablets	79	19	29	10	21
Vitamin E and methyl testosterone tablets	7	1	6	...	...
Local corticosteroid injections and gonadotrophin	2	...	2	...	...
Local corticosteroid injections, methyl testosterone and Vitamin E	2	1	...	1	...
Vitamin E, prednisolone and methyl testosterone tablets	2	1	1	...	...
Local corticosteroid injections, nicotinic acid tablets and Vitamin E	1	1	...	...	...
Local corticosteroid injections, X hyalouronidase and nicotinic acid tablets	1	...	1	...	...
Nicotinic acid tablets	2	...	1	1	...
Improved without treatment	1	...	...	...	...
Treatment postponed	2	...	...	...	...
Result not known	1	...	...	...	...
Defaulted	2	...	...	...	...
No treatment	4	...	...	...	...
Notes not available	2	...	...	...	...

In the younger groups, 12 corticosteroid local injections were given at 2-weekly intervals. The middle-aged groups were treated similarly with the addition of 200 mg tablets of vitamin E twice daily for a period of 6 months.

In the majority of cases the corticosteroid used was dexamethasone sodium phosphate (Decadron) 4 mg per ml and 1·5 ml of this + 1 ml 1% procaine were injected slowly. There is no doubt that since this procedure has been adopted the results, both immediate and late, have been

Table VI

Operation for Calcified Plaques

Good result	1
Considerable improvement	1
Partial impotence	1
Condition unchanged	1
Operation elsewhere, result not known	1

considerably improved especially in younger patients with a short history. The pain, which is probably due to oedema of the ground substance and proliferation of fibroblasts, gradually subsides and the plaques become narrower and softer after a time. The use of several local injections is not acceptable to some patients; others are unable to attend regularly for treatment. As an alternative, 6 local injections are given and patients continue treatment with prednisolone tablets 5 mg 2 or 3 times a day for a period of 2 to 3 months with gradual reduction of dosage.

A number of patients were treated with oral prednisolone only as suggested by Ashworth (1960) with some favourable results.

Vitamin E, 200 mg twice daily for a period of 6 months was prescribed to patients over 58 years of age and when corticosteroids were particularly contra-indicated, as in peptic ulcer or diabetes; the results in these cases were less favourable.

The surgical removal of plaques is rarely accepted by patients and was advised only when the plaques were extensive and calcified (see Table VI).

Treatment with Procarbazine. Following the reports by Aron (1968) of the efficacy of procarbazine (Natulan) in the treatment of Dupuytren's contracture and by Aboulker and Benassayag (1970) of its efficacy in the treatment of Peyronie's disease, it was decided to use the drug on a number of patients in the present series. Procarbazine is a monoamine oxydase inhibitor so that the usual precautions have to be taken during its administration. Blood diseases, kidney and liver dysfunctions are contra-indications to treatment with procarbazine. Alcohol must be prohibited and no other drugs taken. The patient is given an M.A.O.I. card listing the dietetic restrictions.

Procarbazine is given for a period of 3 months on an out-patient basis in 50 mg capsules twice daily after meals. Blood counts have to be carried out weekly to control the dosage. Leucopenia, as shown by a total white cell count of less than 3,000/cu.mm and thrombocytopenia with a platelet count of less than 100,000/cu.mm are indications to stop treatment. The damage to haemopoiesis can be avoided by combining the treatment with prednisolone 5 mg twice daily for 3 to 4 weeks. This method was adopted whenever the white cell count dropped to 4,000/cu.mm or the platelets below 200,000/cu.mm

Nausea, vomiting and headaches were alleviated by metachlopramide monohydrochloride (Maxolon, Primperan) 10 mg tablets 3 times a day before meals.

There is experimental evidence that the drug can cause damage to the germinal epithelium of the testes and in 3 patients in the series there was complete azoospermia at the termination of the course of treatment which was still present 3 months later. This is not considered to be a therapeutic contra-indication though it is probably better to restrict the use of the drug to patients who do not contemplate an increase in their family, and in view of the disordered spermatogenesis to advise them to have a vasectomy.

The results are indicated in Table VII. Improvement is usually noticed in 4 to 6 weeks when the pain usually subsides and the plaques become softer. At the termination of the course of treatment the plaques are shorter, narrower and thinner. Deviation progressively diminishes and the patient is able to resume normal marital life. A second course of treatment can be

Table VII

Response of patients to treatment with Procarbazine (Natulan)
Number of Patients = 24

	Age (years)	*Number of Patients*	*Duration of Symptoms in months*
Good results (11 patients):	28	1	8/12
	30	1	4/12
	40-49	6	3/12-12/12
	52-56	3	6/12-12/12

Partial improvement: 3 patients
No improvement: 4 patients (one with calcified plaque)
Intolerance to drug: 3 patients
Result not known: 1 patient (excision of plaque bone formation)
Defaulted: 1 patient (History of ulcerative colitis. Colectomy)
One patient, age 45: 3 months course of Natulan +6 local injections of Decadron. Good result

prescribed after a rest period of 4 weeks. This enables the bone marrow, gastrointestinal tract epithelium and immune systems to recover.

Review of the Literature

Incidence. Frank and Scott (1971) mention over 2,000 cases recorded in the literature. The disease is comparatively uncommon, but the number of patients referred for treatment has risen steadily in recent years.

Histopathology. The fundamental changes have been described by Pugh (1960) and by Gallizia (1966). The normal tissue is directly continuous with areas in which there is a loss of clear demarcation between erectile tissue and tunica albuginea. There is a fibroblastic proliferation with a variable cellular response and moderate or dense collagen formation depending on the stage of the disease. Smith (1966) found an incipient vasculitis and initial lesions in the thin areolar connective tissue sleeve between the corpora cavernosa and the tunica albuginea. A notable perivascular cuffing with lymphocytes and plasma cells is observed in the early stages. Residual perivascular infiltration is found in the later stages showing fibrosis and hyalinisation.

Collagen containing matrix could induce a calcification process. Serre *et al.* (1969) believe that hyaline degeneration of the ground substance could initiate the changes in advanced cases of collagen disease. Bone formation is not an inherited or atavistic phenomenon; it is preceded by pathologic changes in the tissues (Ruth—see Willis, 1962; Eglitis, 1953; Bett, 1952). An extensive literature exists on the os penis or baculum in many of the species of the animal kingdom, but no authentic case has been found in man. Earlier reports on bone formation by McClellan (1827) and Merle (1899) were based on operative findings or clinical observation respectively. Furuta (1924) found calcification and sclerosis of the dorsal artery of the penis and 2 osseous plaques in the tunica albuginea. The arteries supplying the corpora cavernosa were of normal elasticity and structure. Vermooten (1933) published a case of metaplasia with bone and marrow formation in the glans resulting from a gunshot injury.

Merklen (1954) described 4 cases of plantar fibromatosis—disease of Ledderhose (1897)—and Peyronie's disease. A typical thickening and contraction can be felt in the inner portion of the plantar fascia of both feet. The thickenings in the soles are not painful. Both feet show some degree of cavus (Table III).

Electron microscopy studies show tissue changes similar to those seen in senescence and senility. The feeble cellular changes in fact resemble a more degenerative process than an inflammatory reaction, and it is interesting to note that the concept of precocious senile changes in the penile tissues was suggested by Tuffier (1885).

Clinical Features. These are well known and are described with clarity and precision by Wolfromm *et al.* (1960), Baines (1965), Pyrah (1967) and McRoberts (1969).

The differential diagnosis must include thrombosis of the dorsal artery of the penis, leukaemic infiltration of the corpora cavernosa, thrombosis of the corpora cavernosa caused by hereditary haemoglobinopathies, benign and malignant primary and secondary tumours.

Aetiology. There is no certainty as to the exact nature of the biochemical agencies which appear to initiate the disorder and distort at the macromolecular and cellular level, the histological and histochemical balance and harmony of various components of connective tissue. This phase is not accomplished without considerable cell and capillary reaction and the changes that follow may be said to constitute the characteristic pathology of the disease. A correct pattern of structure is important in connective tissue sheets that cover and preserve the distinct surface contour of an organ. In normal conditions the structure of the tunica albuginea, the septum and the adjacent fascial layer are adjusted to accommodate the highly specialised tissues of the corpora cavernosa. Fitton Jackson (1968), Woessner (1968) and Herbst (1958) indicate that the specific structural proteins must be synthetised in a consequential manner and their equilibrium is maintained by hormones, enzymes, vitamins and nervous control. Crick (1965) has thrown considerable light on the way in which the genetic information is transmitted to the protein making machinery of the cell. di Macco (1966) considers the possibility of a hereditary factor in Peyronie's disease.

Gallizia and Gallizia (1972) consider the possibility of a systemic character of the disease. They postulate an inertia of the pituitary, vulnerability of the adreno-cortical system and functional predominance of the zona glomerulosa would cause an increased vascular and connective tissue reactivity in collagen diseases. However, the single estimations by the authors of plasma corticosteroids can hardly be considered as a reliable criterion of adrenocortical function, for example the time of day at which samples are taken is of major importance, morning readings being more conclusive.

Barrett (1958) does not regard Peyronie's disease or Dupuytren's contracture as systemic collagen diseases. He stresses the absence of systemic and inflammatory elements, their purely localised character and non-involvement of the neighbouring areas.

As discussed earlier, the suggestion that the condition has an autoimmune basis is gaining favour.

Treatment. Asböe-Hansen and his collaborators (1966) discuss the effects of corticosteroids on the cellular and fibrillar elements of connective tissue and on the ground substance. Doherty and Berliner (1968) indicate the relative potency of different preparations of corticosteroids on growth inhibition of fibroblasts.

The phases and stages by which our knowledge has advanced and the rationale of combination therapy with vitamin E and local corticosteroid injections have been outlined in previous papers by the writer (Chesney, 1960, 1963 and 1966), Eckström and Hultengren (1962), Ducassou (1966), May and Hirtl (1966) and Desanctis and Furey (1967) have obtained favourable results with a similar method of treatment.

The first successful operation for ossification of the septum was carried out by McClellan (1827). Lowsley and Boyce (1950) write with confidence on results achieved in 50 patients Fogh-Andersen (1957) in a series of 8 patients recorded an excellent result in 2, a marked improvement in 4 and a moderate improvement in 2 patients. Similar favourable results were reported by Balogh and Köves (1969) in 4 patients. Poutasse (1971) reports on a modified technique of operation in 36 patients with only a few complications in the postoperative period.

Griff (1967) reports on patients who were treated with a specially designed radium mould. A typical treatment was 1,500 mg hours delivering 1,200 r to the skin within a 10-hour period.

Hasche-Klunder (1970) writes on long term oral use of potassium paraminobenzoate (Potaba) with impressive improvements. Aquino, Cunningham and Filbea (1967) obtained good results with Cobalt 60 teletherapy. A dose of 700 rads was given in a single treatment and pain quickly subsided. Toksu (1971) used a Dermo-jet to inject corticosteroids. The Dermo-jet is a needless pressure injection which produces a high-velocity microspray and painless tissue injection.

An alternative approach to the problem of therapy was made by Aron (1968), who treated Dupuytren's contracture with the methyl-hydrazine derivative—procarbazine (Natulan). This cytostatic drug was effective in 8 patients. Aboulker and Benassayag (1970) treated 17 patients with Peyronie's disease. Nine patients were cured, 6 improved, 1 failed to improve and in 1 case treatment was interrupted. Experimental data have been reviewed by Bollag (1965) and studies on the mode of action were carried out by Brookes (1965).

Discussion

There is a divergence of opinion on one vital question—should the disease be treated? As with many other conditions remissions may occur, from time to time, often unpredictably. Williams and Thomas (1970) observed that very little difference in results has been noticed between 12 untreated patients and 9 patients submitted to radiotherapy. Byström *et al.* (1972) describe the results of 4 methods of treatment in 58 selected cases. They conclude that conflicting reports on therapy are an indication that no method is fully successful. Übelhör (1966) reported that in reply to a questionnaire 39 authors considered local steroid injections as the therapy of choice. Thus there are two opinions, utterly divergent, equally supported by experience and ethics. In a situation that has become stressful to both husband and wife speedy improvement is so important that probably effective treatment is advised in all cases. It is hardly desirable for a middle-aged man to await spontaneous improvement or even cure in the 4 years reported as the average time for resolution by Williams and Thomas (1970). The personal experience described in this paper is strongly in favour of treatment.

Conclusions

There is clinical and statistical support for those who advise treatment.

Although in even the most successful cases, the lesions seldom completely resolve, the methods of corticosteroid therapy are safe and produce results which are generally satisfactory. Corticosteroids given locally or even systemically for a limited period of time are unlikely to suppress endogenous adrenal activity. The relatively speedy response in our series—6 to 12 months—differs greatly from the improvement or cure as a sequence of the natural history of the disease.

Summary

The history and clinical features of Peyronie's disease are briefly reviewed.

The results of treatment with procarbazine ("Natulan") are presented.

It is concluded that treatment with procarbazine is often effective and is indicated in a selected group of patients, provided the appropriate precautions in its use are undertaken.

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Treatment of Peyronie's Disease with Procarbazine

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Procarbazine is a cytotoxic drug which is especially active against Hodgkin's disease and, with more inconstant success, against other malignant lymphomas. Aron (1968) noted a regression of Dupuytren's disease in a patient under treatment with procarbazine for Hodgkin's disease. He suggested the use of this agent in diseases with proliferation of the connective tissue. In 1970 Aboulker and Bennassayag reported their excellent results with procarbazine in the treatment of Peyronie's disease. Comparable results were published subsequently by other French investigators (Sturm and Lebeuf, 1971). These enthusiastic communications incited us to test procarbazine in patients with induratio penis plastica.

Materials and Methods

As procarbazine is a cytotoxic drug certain precautions must be taken. A regular control of leucocytes and platelets must be carried out. When this count is lower than respectively 3,000 and 100,000 per cmm, treatment must be interrupted temporarily. Alcohol intolerance may develop, and therefore abstinence is necessary. Potentiation of the action of barbiturates, phenothiazides and imipramine-like drugs may occur. In diabetic patients procarbazine may produce a rise of the blood sugar. Procarbazine can have a noxious effect upon spermatogenesis.

Ten patients (see Table I), suffering from Peyronie's disease were treated with 100 mg procarbazine daily (1 × 50 mg tablet after meals twice a day). We planned to give the drug during a period of 3 to 5 months, as had been suggested by Aboulker and Bennassayag (1970).

Table I

No.	Age (years)	Duration of disease before treatment	Duration of procarbazine treatment	Results	Side-effects
1	44	5 months	90 days	unchanged	none
2	66	2 years	75 days	unchanged	none
3	56	3 months	53 days	unchanged	rash, disturbances of equilibrium
4	61	1 year	90 days	unchanged	none
5	41	5 days	27 days	completely cured	agitation, insomnia
6	63	3 years	60 days	unchanged	none
7	63	2 months	150 days	unchanged	none
8	52	1,5 year	60 days	unchanged	none
9	61	2 years	21 days	unchanged	none
10	43	1 year	120 days	unchanged	none

Results

The results are listed in Table I. Only 1 patient (no. 5) was completely cured. We doubt however that he really was a case of Peyronie's disease.

His complaints started very suddenly: pain during erection for 5 days which made intercourse impossible. There was no history of trauma to the penis. Clinical examination revealed a hard nodule in the septum just behind the glans. The subjective complaints disappeared after 1 week of treatment and the nodule after 4 weeks. Therapy was stopped after 27 days. Two years later he is still symptom free.

In 9 other patients neither the subjective nor the objective signs of the disease were ameliorated. Only 4 patients continued the therapy during 3 months or longer. In patient no. 3 the medication was stopped for recurrent and serious side-effects. Patients no. 2, 6 and 9 stopped taking the therapy earlier than 3 months because there was no sign of improvement.

Four patients who had a concomitant Dupuytren's contracture showed no improvement of this lesion after treatment.

Side-effects were serious in 2 patients. Patient no. 3 developed a generalised rash with oedema of the eyes and the face with slight disturbance of equilibrium. These symptoms reappeared when medication was recommenced. Patient no. 5 showed nervous tension and insomnia.

Discussion

Our results of the treatment of Peyronie's disease with procarbazine, 100 mg daily, are disappointing. Even in this reduced dose (the normal anti-tumour dose is at least 200 mg daily) side-effects occurred. In many instances the patient himself stopped the therapy after 1 or 2 months because of the absence of any improvement.

Conclusion

We have discontinued the treatment of Peyronie's disease with procarbazine because we obtained no encouraging results. In addition we fear to give a cytostatic drug for a benign disease.

Summary

The treatment of 10 cases of Peyronie's disease with procarbazine, a cytotoxic drug, is presented. The results were disappointing.

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ABSTRACTS FROM CURRENT UROLOGICAL LITERATURE

Annales Chirurgiae et Gynaecologiae Fenniae

By J. V. Mandel

"Results of the Wertheim Operation with Special Consideration of Complications of the Urinary Tract." Anni Helo. (1965, **54**, 320–436.)—The results of 449 Wertheim operations, considering the complications of the urinary tract, are reported. The primary mortality was reduced from 8·6 to 2%. Uretero-vaginal fistulae occurred in 8·1% of the patients. Secondaries in lymph glands were detected in 5·05%. Late complications can be found by X-ray investigations, therefore i.v. urography should include follow-up examinations.

"Transvesical Prostatectomy A. M. Hryntschak." I. Arvola and H. G. Lilius. (1972, **60**, 74–78.)—Suprapubic prostatectomy following the so-called Hryntschak's modification of Harris' method was performed on 416 patients. After enucleation of the adenoma, a wedge incision was made into the bladder neck, and after insertion of a catheter the bladder neck and the prostatic cavity were closed with transverse catgut sutures. Mortality was 3·1%, incidence of incontinence 1%. Incontinence was complete in 2, and mild in another 2 patients. Significant stenosis of the bladder neck was observed in 1·7% of patients. Wedge excision of the bladder neck is important to prevent stenosis. Bladder wash-out for secondary haemorrhage had to be done on only 0·7% of patients.

"Transurethral Prostatic Resection." I. Arvola and H. G. Lilius. (1972, **60**, 79-82.)—Transurethral prostatic resection was performed on 229 patients for benign prostatic hyperplasia. Mortality was 1·7%. Reresection was done in 15·3%. The prostatic capsule was perforated in 5 cases (2·3%) and suprapubic drainage was instituted in 3 of them. Secondary bleeding occurred in 4·8%, during the first 2 post-operative weeks. Incontinency occurred in 2·6%, urethral stricture in 2·4%, strictures of the penile urethra in 1·9%, and stenosis of the bladder neck in 1·4%. Complete prostatic resection is necessary for good results. Small, medium sized and especially fibrotic prostates are suitable. Open surgery is better for large prostates.

"Renal Tuberculosis." I. Arvola, H. O. Lilius and T. Kalima. (1972, **60**, 83-86.)—This series consists of 92 patients, suffering from renal tuberculosis, in the seventh decade of this century. The symptoms and signs were frequency of micturition, dysuria (38·8%), sterile pyuria (20·4%), epididymitis (18·3%), renal colic (9·7%) and macroscopic haematuria (8·5%). In 44·5% treatment was with anti-tubercular drugs only. Nephrectomy was done in 36·5% of patients. The indications for surgery were: non-functioning kidneys, large hydronephroses caused by stricture, macroscopic haematuria, suspicion of malignancy, and renal pain. Pyeloplasty was performed in 3 patients, reconstruction of uretero-vesical junction in 4, and dilation of the ureter in 6 patients. In 8 patients the disease recurred within 2 to 6 years, after conclusion of treatment.

"Further Experience with the Franzen Transrectal Prostatic Biopsy Needle." J. P. Ward. (1974, **63**, 48-52.)—152 transrectal prostatic biopsies were performed on 145 patients between 1968 and 1972, in 2 London teaching hospitals. The Franzen needle was used for that purpose. The cytological diagnosis was compared with the histological diagnosis in 48 patients, and 20% non-correlation of the results was demonstrated.

These differences are discussed in detail. The diagnosis of carcinoma of the prostate was missed, using the Franzen needle, in 7 patients, and in 3 patients histological examination of the fragments, after transurethral resection. 7·9% of the cytological preparations were unsatisfactory for diagnosis.

In this series the Franzen needle biopsy was correct, in 85% of the investigations.

"Spontaneous Rupture of a Renal Artery Aneurysm with Survival." H. G. Lilius. (1972, **60**, 128-129.)—A case of spontaneous rupture of an aneurysm of a renal artery, with survival, is reported.

Surgery, Gynecology and Obstetrics

By Thomas Moore

"Non-functioning Carcinoma of the Adrenal Cortex". Alan R. Shons and William G. Gamble. (1974, **138**, 705–709.)—From the Department of Surgery, University of Minnesota and the St Louis Park Medical Center, Minneapolis, the authors report 6 cases varying in age from 52 to 77 years; 4 were male. The most frequent presentation was localising pain, abdominal mass and kidney displacement shown on intravenous or retrograde pyelography. Adrenal angiography, although difficult, can differentiate adrenal from renal lesions. Histological examination confirms the malignancy of the tumours and few patients survive more than 5 years. The authors recommend treatment by wide en bloc excision through a transabdominal approach. Radiotherapy is non-effective but ortho, para DDD chemotherapy (1,1-dichloro-2-(0-chlorophenyl)-2-(p-chlorophenyl)-ethane) can give some short term palliation.

"Large Volume Diuresis as a Mechanism for Immediate Maximum Renal Function after Transplantation." Arnold G. Diethelm, Joaquin S. Aldrete, William A. Sterling and Jean M. Morgan. (1974, **138**, 869–874.)—From the University of Alabama the authors report their results in 50 consecutive patients who have received renal transplants from living donors. Mannitol was used as an osmotic diuretic in both the donors and recipients. The graft had immediate function in 98% of the cases and 92% were functioning normally 1 year after operation. None was lost because of rejection. The immediate diuresis caused a rapid fall of serum creatinine. In 70% it was less than 2 mg per kg 48 hours after transplantation. Only 1 patient required dialysis in the first postoperative week, but recovered satisfactory long-term renal function. A cold ischaemic interval up to 52 minutes or less did not seem to affect kidney function in the postoperative period.

"A Fibrinogen-free Plasma Perfusate for Preservation of Kidneys for one Hundred and Twenty Hours.'. Luis H. Toledo-Pereyra, Richard M. Condie, Rickard Malmberg, Richard L. Simmons and John S. Najarian. (1974, **138**, 901-905.)—Silica precipitated plasma is cholesterol-, fibrinogen-, alpha-lipoprotein- and beta-lipoprotein-free and has only about one-third of the triglicerides. The authors have shown that dogs survive better and have better renal function, after autotransplantation and contralateral nephrectomy, when the kidney has been perfused with silica-precipitated rather than cryo-precipitated plasma. Two of 8 kidneys perfused with it for up to 120 hours have recovered normal function within 18 days.

"Factors Involved in Discarding Cadaveric Kidneys Preserved by Machine Perfusion." Thomas C. Moore, Thomas S. English, A. J. Conovaloff, Thomas V. Berns and Carlos A. E. Lemmi. (1974, **138**, 545-548.)—The authors point out that one of the ways of increasing the supply of cadaveric kidneys for transplantation is to avoid wastage through mistakes in removal from donors and also their efficient machine preservation. They report results from the Greater Los Angeles Mobile Kidney Preservation Unit for the first 27 months of its existence. 334 human cadaveric kidneys from 178 donors were preserved by the Belzer machine perfusion with cryo-precipitated human plasma under oxygenated hypothermia. 278 of these kidneys were transplanted and 56 were discarded. The authors analyse in detail the reasons for non-transplantation which they classify as follows:

Good reasons (29)	
Poor or borderline perfusion	23
Accidental injury to, or contamination of kidney	4
Donor disease discovered at autopsy	2
Borderline reasons (6)	
Harvesting damage to kidney	6
Questionable reasons (21)	
Unfounded concern with perfusion flows and pressures	10
No local recipients	5
Multiple vessels or ureters	4
Donor creatinine level elevated	2

In discussion, the many factors considered include haemodialysis, the pre-mortal treatment of the donor and the warm ischaemic time. The ideas presented must be of considerable value to those actively engaged with the problems of renal transplantation.

"Malignant Tumours of the Renal Pelvis." Harry S. Latham, and Saul Kay. (1974, **138**, 613-622.)—These two pathologists from the Department of Surgical Pathology, Medical College of Virginia, Richmond, present a detailed review of the literature with 57 references. Transitional cell carcinoma, squamous cell carcinoma, adenocarcinoma and sarcoma are considered. 25 cases of carcinoma of the renal pelvis examined in their department during the last 20 years are discussed in great detail. Included are the oldest to be reported, 92 years of age, 1 of bilateral tumour and 1 long-term survival, nearly 5 years following nephrectomy for squamous cell carcinoma in which local invasion of vessels had occurred.

"Early Post-transplant Function of Machine-preserved Cadaveric Kidneys in Sensitized Recipients." Thomas C. Moore, Thomas V. Berne, Thomas S. English and Carlos A. E. Lemmi. (1974, **139**, 45-48.)—In the greater Los Angeles area, 47 machine-preserved cadaveric human kidneys were transplanted into presensitised recipients whose sensitisation had been detected at some time prior to transplantation by the presence of cytotoxic antibodies against 10% or more of a pool of approximately 100 donor cells. Detailed study showed that those patients having a short period of haemodialysis were proportionately less sensitised. The degree of sensitisation in patients undergoing haemodialysis was in direct proportion to the length of time during which haemodialysis had been carried out, as was the subsequent function of the transplanted kidney.

"Stenosis of the Renal Artery and Coexistent Lesions." Joseph J. Kaufman, Leonard S. Marks and Robert B. Smith. (1974, **139**, 59-64.)—During a 10-year period at the UCLA Hospital, Los Angeles, 350 patients were operated upon for renovascular disease. 13 patients, aged from 21 to 64 years, of whom 7 were female, were found to have stenosis of the renal arteries with coexisting renal or adrenal disease. In 6 there was a space occupying kidney lesion, 4 suffered from inflammatory lesions and 3 had adrenal tumours. The cases are reported in some detail and the diagnostic and therapeutic problems discussed.

"Supravesical Urinary Fistulas after Transplantation." William H. Hoch, Layton Kest, Sidney Cohen, Kenneth Newark and Lester Peesky. (1974, **139**, 82-86.)—The authors from Cleveland Ohio, report the problems encountered in 9 patients who developed non-vesical fistulae after renal transplantation. The problems of diagnosis, investigation and treatment are discussed and prompt and aggressive management recommended to save both the life of the patient and the allograft.

Collective Reviews.

"Fibromuscular Dysplasia". M. O. Perry. (1974, **139**, 97-104.)—The author reviews the literature in considerable detail and gives 46 references. Although the disease is a generalised arteriopathy it is most common in the renal arteries and the review is much concerned with this site.

"Efficacy of Radiocholesterol Imaging of the Adrenal Glands in Cushing's Syndrome." DAVID C. MOSES, DAVID E. SCHTEINGART, MARTIN F. STURMAN, WILLIAM H. BEIERWALTES and RODNEY D. ICE. (1974, **139**, 201-204.)—The authors detail the method used in the Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor. They believe that it is a valuable tool in the detailed differential diagnosis of adrenocortical lesions causing Cushing's syndrome, making angiographic techniques unnecessary for the localisation of adenomas. It is reliable in identifying functioning adrenal remnants and helpful in distinguishing bilateral adrenal hyperplasia from adenoma.

"Effects of Blood Transfusions on Antibody Formation and Canine Renal Allograft Survival." CHARLES B. CURRIER, Jr. and JAMES C. PIERCE. (1974, **139**, 241-244.)—The authors stress the value of renopathy in screening patients with pelvic tumours for ureteric obstruction. They quote their experience in 54 patients with carcinoma of the cervix; 19 with carcinoma of the bladder, 17 carcinoma of the endometrium, 8 carcinoma of the ovaries and 2 carcinomata elsewhere. When obstruction has been diagnosed, intravenous urography can better delineate the site and extent of the obstruction.

Annals of Surgery

"Ureteral Obstruction Secondary to Aortic Femoral Bypass." A. F. PETRONE, P. J. DUDZINSKI and W. MANIATIS. (1974, **179**, 192-196.)—This paper reports the authors' observations on 4 patients who presented with urinary dysfunction following aortic femoral bypass surgery. Three patients presented with a history of out-flow obstruction whilst the fourth patient had no genito-urinary symptoms. Ureteral observation was found only because excretion urography was an integral part of the evaluation of these patients. In 2 instances the ureter was mechanically compressed by the rigid graft in addition to evidence of periureteral fibrosis.

The authors recommend that the ureter should be placed anterior to the graft to avoid compression and that, when obstruction has occurred, treatment should be by division and transposition of the ureter with reconstruction anterior to the graft.

The occurrence of silent obstruction indicates the value of follow-up excretion urography in these patients.

"Bladder Dysfunction and Its Manifestations Following Abdominoperineal Extirpation of the Rectum." M. KONTTURI, T. K. I. LARMI and S. TUONOEN. (1974, **179**, 179-182.)—The authors report the investigation of 13 patients who had undergone abdominoperineal extirpation of the rectum 6 months to 5 years previously together with a control series of a further 29 patients following other urogenital or pelvic operations. Cystometry was normal in 6 patients, hypotonic in 5 patients and hypertonic for 2 patients both of whom had infection. None of the patients showed complete denervation of the bladder.

Urinary flow measurements by the Kaufman uroflometer revealed a significant reduction in flow following abdominoperineal resection compared with the control series.

The results confirm that impaired emptying of the bladder in varying degree and infection were frequent late complications of this operation although many patients may not spontaneously present with symptoms.

The causes of this postoperative dysfunction are discussed and indicate that full urological review even in the asymptomatic patient is necessary. This small series confirms British observations and indicates an appropriate investigative regime.

British Journal of Radiology

By CHARLES NICHOLAS

"Renin-secreting Juxtaglomerular-cell Tumour." J. K. DAVIDSON and D. C. CLARK. (1974, **47**, 594-597). —A rare benign tumour causing hypertension in young people. Six cases have previously been reported. The 7th case reported by the Department of Diagnostic Radiology, Western Infirmary, Glasgow, occurred in a girl of 8 who had occipital headaches, enuresis, thirst, polyuria and hypertension without retinal changes. The plasma renin, aldosterone and angiotensin II were raised but tests for pheochromocytoma were negative. The IVP was normal but an area of relative translucency was seen in the nephrogram phase of a selective renal arteriogram, surrounded by a rind of compressed renal cortex and a bulge in the renal outline. The authors believe this is the first case diagnosed radiologically. Bilateral renal vein samples obtained simultaneously showed a very high renin on the left compared with the opposite side. At operation an encapsulated grey tumour 8 mm diam was found in the lower pole of the left kidney. It consisted of polygonal justaglomerular cells with prominent granules in the cytoplasm and there was intimal and medial thickening in the vessels. The renin content of the tumour was extremely high. 10 days postoperatively the patient's B.P., plasma renin, angiotensin II and aldosterone all returned to normal.

The Journal of the American Medical Association

By D. T. H. PAINE

"Extracorporeal Renal Parenchymal Surgery With Continuous Perfusion." M. J. SULLIVAN, MD; E. JOSEPH, MD; J. C. TAYLOR, MD; Department of Urology, School of Medicine, University of California, Davis. (1974, **229**, 1780-1781.)—A further report on bench surgery for renal disease. The patient concerned was a 41-year-old white woman with hypertension (180/120 mm Hg) with *Proteus mirabilis* urinary infection and a staghorn calculus with many small calculi in the left kidney. There was also an unsuspected fibromuscular dysplasia of both renal arteries, with the right side more severely involved than the left, the right side being the apparent cause of the hypertension. The renal artery was treated with excision of the diseased segment and end-to-end anastomosis. Following the procedure the blood pressure fell only to (140/100 mm Hg). The patient's left kidney was removed through a flank incision flushed with cold lactated Ringer solution containing heparin sodium. Perfusion was maintained with a pulsatile organ-perfusion apparatus (Viacell), using cryoprecipitated filtered human plasma continuously oxygenated and cooled to 9°C. Using long tubing the kidney was placed on an adjacent table remote from the operative field and perfusate so that stone fragments would not fall into it. A lower pole partial nephrectomy and extended pyelotomy afforded sufficient exposure to remove the staghorn calculus and meticulously remove fragments and irrigate out the calyces. A fiberoptic light cord was also used to aid in this manoeuvre. X-ray films demonstrated complete removal of all fragments. Following this the kidney was repaired and the diseased segment of the main artery excised. Re-implantation of the kidney into the right iliac fossa was carried out using standard techniques with ureteroneocystostomy. The total ischemia time was 5½ hours. The kidney functioned immediately and the patient recovered uneventfully and was discharghed on the 12th postoperative day. The patient's creatinine clearance, which had previously been 83 ml/min was 106 ml/min on the day of discharge. Four months later the patient was normotensive (120/70 mm Hg), with uninfected urine.

"Splenectomy in Renal Transplantation." H. M. Kauffman, M. K. Swanson, W. R. McGregor, R. E. Rodgers and P. S. Fox. (1974, **139**, 33-40.)—Contrary to the opinions of other transplanters, the authors from Milwaukee, Wisconsin, believe that hypersplenism occurs in chronic renal failure. In their experience the results of renal transplantation are better if the patients have the spleen removed as a first stage. The poorer results in the absence of splenectomy they believe are due to the leucopenia associated with the hypersplenism. However the results are also improved by splenectomy at the time of transplantation. As studies of the differences in the total white blood counts and polymorpholeucocyte counts in the splenic artery and vein were similar in both, the authors believe mechanisms, at present not understood, are responsible for the difference in the results.

APOLOGY

We regret that two diagrams in Figure 1 in Mr Johnston's paper *Lengthening of the congenital or acquired short penis* on page 685 in the December 1974 issue were printed upside down.

Conferences and Courses

INTERNATIONAL SYMPOSIUM ON PYELONEPHRITIS

The 3rd International Symposium on Pyelonephritis will be held at the Royal College of Physicians in London on 21st, 22nd and 23rd July 1975. Attendance will be limited to participants actively working in the field of pyelonephritis. Application forms are obtainable from the Secretary to the Organising Committee:
Dr Donald A. Leigh,
Department of Medical Microbiology,
Wycombe General Hospital, High Wycombe,
Buckinghamshire, England.

BRITISH ASSOCIATION OF PAEDIATRIC SURGEONS

XXIInd ANNUAL INTERNATIONAL CONGRESS

Newcastle upon Tyne, 30th July to 1st August 1975

The paediatric urology section of the Scientific Programme will be held on the afternoon of Friday, 1st August.

The Executive Committee of the British Association of Paediatric Surgeons have kindly invited members of BAUS to attend this section.

Members who wish to attend should apply to the Congress Secretary, BAPS, University of Newcastle upon Tyne, Department of Surgery, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP. There will be no fees involved for BAUS members attending only the urology section.

INTERNATIONAL MEETING ON THE HORMONAL THERAPY OF PROSTATIC CANCER

DEPARTMENT OF UROLOGY OF THE UNIVERSITY OF ROME

President: Professor U. BRACCI.

The meeting will be held in Rome on Friday and Saturday 23rd, 24th May 1975.

Many foreign speakers have been invited.

A full programme will be circulated later: the provisional arrangements are as follows:

Friday, 23rd May 1975
Morning session

(1) PATHOLOGIC ANATOMY
- (*a*) Histological types of the prostatic cancer.
- (*b*) Tumour evolution in relation to the histological type (local invasion and diffusion, metastases).

(2) HORMONE DEPENDENCY
- (*a*) Fundamentals of the hormone dependency.
- (*b*) Hormone dependency and histological types of the tumour.

Afternoon session

(3) PLASMATIC ANDROGENS
- (*a*) Sources.
- (*b*) Androgens and their metabolism.
- (*c*) Receptors.
- (*d*) Testosterone metabolism in the prostate

Saturday, 24th May 1975
Morning session

(4) HORMONAL THERAPY
- (*a*) Informing principles.
- (*b*) Parameters evaluating the effects of hormonal therapy.
- (*c*) Different hormonal therapies:
  - —castration: efficacy and disadvantages;
  - —oestrogens: efficacy, disadvantages and oestrogen-resistance;
  - —anti-androgens: efficacy and disadvantages;
  - —adrenalectomy and hypophysectomy: efficacy and disadvantages.

Afternoon session

(5) THERAPEUTIC ASSOCIATIONS AND THEIR INDICATIONS

Discussion.

Concluding remarks on the present position of hormonal therapy.

Secretarial Department and General Information

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Travel arrangements, Hotel and Hostel Accommodation

Details of travel arrangements and booking for hotel and hostel accommodation can be made through

Wagons-Lits/Cook
Via Gradisca, 29
00198 ROMA

Book Reviews

The Treatment of Prostatic Hypertrophy and Neoplasia. Edited by J. E. CASTRO. Pp. 200. Lancaster: Medical and Technical Publishing Co., Ltd. 1974. £6·75.

This book is a collection of 7 essays on the biology, endocrinology and treatment of prostatic disorders. Its contents will mostly be familiar to urologists. The first 2 essays on the biology of the prostate (Franks) and medical treatment of benign hyperplasia (Geller) form a useful introduction to the subject and assemble a mass of information which tends to remain scattered in the journals and is seldom brought together in one place. It would be easy—and unfair—to criticise essays on the medical management of benign hyperplasia: the subject is in its infancy. There is, however, one serious omission, which is inherent in a book such as this, which does not discuss diagnosis. Benign hyperplasia is by no means the only cause of "prostatism" and surely some attempt should be made to differentiate the conditions for which "prostatectomy" is performed.

Essays by Chisholm and Hendry give excellent critical accounts of corrective treatment of the malignant prostate and the use of adrenalectomy and hypophysectomy. It is not their fault that the proponent of any form of treatment will find evidence to support his viewpoint. These authors are sensibly reluctant to be dogmatic.

The remaining essays, on the surgery of benign disease (Mitchell), cryosurgery (Green) and radical prostatectomy (Flocks) present standard accounts of treatment. Rather a lot of operation detail is given: too much for the non urologist, not enough for the practising surgeon. Perhaps the value of the book would be enhanced if some of this space were used for further discussion on those obscure aspects of pathology or treatment.

On the whole, this is a useful book. It is pleasantly written and easy to read, though it is slightly irritating to see spellings "tumor", "estrogen", etc., in a British book.

D. M. E.

Living or Dying—Adaptation to Hemodialysis. Edited by NORMAN B. LEVY. 1st Edition. Pp. 145 with no illustrations. Springfield, Ill. Charles C. Thomas, 1974.

This is the first book to be devoted to the psychological and emotional problems of patients receiving regular long-term haemodialysis. Among the contributors are three physicians with an interest in renal disease, one paediatrician, seven psychiatrists and two clinical psychologists. The first chapter consists of a panel discussion by five experts including Dr Belding Scribner, the pioneer of regular haemodialysis as we know it today. The chat is anecdotal and entertaining and serves to introduce some of the problems. Those who have worked in American dialysis units are immediately reminded of the additional anxiety suffered by patients because of the financial hardship which prolonged and expensive illness may cause. The book goes on to describe various studies of the psychological adaptation to haemodialysis by different groups of patients.

The authors have shown that formal psychiatric assessment of patients prior to starting dialysis has some predictive value as to how they will react on dialysis though there is a tendency to overestimate patients' ability to adjust. Depression and feelings of hopelessness may result in behaviour which can only be interpreted as thinly disguised attempts at suicide. Frequent "accidents" or inability to adhere to dietary regimes or fluid restriction are more likely to be due to low morale than lack of intelligence. Clear cut suicidal behaviour such as deliberately disconnecting shunts or blood lines are surprisingly uncommon.

A nationwide survey of sexual adjustment to haemodialysis confirms one's impression that males are generally impotent and females have no desire. A greater cause for disillusionment are figures purporting to show that the situation does not significantly improve after successful renal transplantation.

There are good sections on the treatment of the child receiving haemodialysis (children tend to remain physically small and emotionally immature), and some of the psychological and social factors determining individual survival on haemodialysis.

For specialists in this field the book certainly provides food for thought. It should be read by all doctors, nurses and social workers who have responsibility for dialysis patients.

P. R. U.

ABSTRACTS OF THE PROCEEDINGS OF THE UROLOGICAL SOCIETY OF AUSTRALASIA

27th ANNUAL GENERAL MEETING, MELBOURNE, 1974

President: K. B. Burnside (Melbourne)
Honorary Secretary: H. Thomas (Sydney)
Editor: G. F. Murnaghan (Sydney)

Franzen Aspiration Biopsy of Prostate

By D. Golovsky, FRACS
Repatriation General Hospital, Concord, N.S.W.

Using a modification of the original Franzen needle of wider diameter a series of 219 aspiration biopsies of the prostate have been carried out upon patients with suspicious areas in the prostate but not previously diagnosed as carcinoma. The biopsies were taken by the transrectal route with the patient lying in the left lateral position and the aspirates were fixed in 95% alcohol and the preparations were stained with haematoxylin and eosin.

75 biopsies gave a positive diagnosis for carcinoma of the prostate, 129 were negative, 6 were recorded to be atypical or suspicious of carcinoma and 9 were unsatisfactory for technical reasons. Of the 129 negative biopsies, 14 were proven positive by other forms of biopsy so that the false negative rate for aspiration biopsy was 6·5%. If only those cases are considered in which an additional form of biopsy was performed then this rate rises to 10%.

Of the positive biopsies only 23 were taken from glands which were hard or fixed compared with 15 such prostates in the series of 129 negative biopsies and 5 of these were among the false negatives. In the entire series the diagnosis of carcinoma on palpation of the prostate was proved accurate in approximately 60% of cases.

Aspiration biopsy has proved rapid and simple to perform without anaesthetic and in the out-patients' department or consulting room. It needs little specialised training to carry out the biopsy but the services of an experienced cytologist are essential for proper interpretation.

The Accuracy of Cytology in Prostatic Carcinoma

By Peter S. Lawson, FRACS
Royal Melbourne Hospital, Melbourne, Victoria

Though clinical assessment of the pathology in a nodule in the prostate is inaccurate, transrectal biopsy using the Franzen needle permits accurate sampling of a particular area of the prostate.

66 patients with clinically suspicious prostates had 82 needle biopsies without anaesthesia and prior to transurethral resection of the prostate. Second and third biopsies were taken in some patients so that overall cytologically satisfactory specimens were obtained from 87% of the patients. No side-effects were noted from the procedure.

When the final histological diagnosis was carcinoma (41 cases) only 2 incorrect cytological diagnoses were made but 10 clinical diagnoses were incorrect.

In those cases where the final diagnosis was benign (25 cases) there was 1 incorrect cytological diagnosis, but 4 incorrect clinical diagnoses.

Among all the patients, the cytological diagnosis was suspicious of carcinoma in 18 patients and in 13 of these 18 the final diagnosis was that of carcinoma of the prostate.

Transrectal prostatic biopsy is simple and safe. It is more accurate than clinical assessment and gives a sound basis for treatment.

Conservative Management of Prostatic Cancer

By W. G. E. Straffon, FRACS
Prince Henry's Hospital, Melbourne, Victoria

We have very incomplete evidence regarding the natural history of early untreated prostatic carcinoma. However, such evidence as is available, plus reasonable speculation, suggests that the life expectancy of a patient with early, histological, or stage I prostatic cancer is measured in decades. Post mortem studies of the prostates of men dying of other disease, when compared with death rates from prostatic cancer, suggest that histological prostatic cancer is 100 times commoner than death from this disease in the same age-group. Even when death rates by age are projected to allow for the presumed long latency of histological cancer, there is still a discrepancy between incidence and death in excess of 20 times. Therefore, there seems to be a strong argument against performing radical surgery in the early stages of a disease which in many cases will not kill the patient. The risks of more conservative therapy are well known; for example the chances of significant thrombo-embolic complications of high dose oestrogen therapy appear to be about 10%. It is therefore suggested that urologists should consider affording no treatment to prostatic carcinoma cases unless the tumour demonstrates aggressiveness. At present the only known reliable index of aggressiveness of a prostatic tumour is its behaviour *i.e.* demonstrable advance of an early tumour or extra-prostatic spread at first presentation.

An ongoing long-term prospective study of prostatic carcinoma at this hospital now uses the above philosophy in its treatment protocol. Stage I and Stage II tumours are not treated unless they demonstrate progression, and thus serve as a study of the natural history of untreated prostatic cancer. Tumours in Stage III and Stage IV (including those associated with elevation of serum prostatic acid phosphatase) are treated. Treatment is monitored by regular measurements of plasma testosterone and pituitary gonadotrophins, as well as more standard parameters, and is analysed by time to failure of treatment instead of time to death. A "clinical score" has been developed to record the progress of the patient and his cancer. This method facilitates short-term trials of various treatment modalities by taking into account both their efficacy and their complications.

It is hoped that over 10-15 years this study will provide not only information about the natural history of early untreated prostatic cancer, but also reliable statements about the advantages and disadvantages of a number of treatment modalities in prostatic carcinoma.

Irradiation Treatment of Prostatic Carcinoma

By S. G. STENING, FRCS, FRACS
Royal Brisbane Hospital, Brisbane, Queensland

During the 5-year period from 1967 to 1971 56 men with prostatic carcinoma were treated by external supervoltage radiotherapy to the prostatic region. Each patient received 5,500 rads using 3 small fields, 1 anterior and 2 posterior oblique.

Patients were referred for irradiation when it was considered that the disease was confined to the prostate glands or had only limited extracapsular spread and when the serum acid phosphatase level was normal and there was no radiological evidence of skeletal metastases. The prostatic lesions were classified on clinical examination as nodule (4), diffuse (38) and extracapsular (14). Material for histological diagnosis was obtained at transurethral prostatic resection (32), open prostatectomy (12) or from needle biopsy (12).

Of the total series of 56 patients, 3 have died of causes other than prostatic carcinoma but within 2 years of treatment; they were each considered to be free of tumour at the time of death. 5 patients have been lost to follow-up whilst 26 of the remaining 48 patients have failed to respond to therapy.

Of the 26 failures, metastases have developed in 17 and the primary tumour has progressed in 9 patients; all of these failures have occurred within 3 years of treatment and most of them within 2 years.

22 patients are clinically free from carcinoma and 18 of these 22 have remained so for more than 3 years so that most of them should have a good chance of long-term cure.

Significantly more failures to respond to therapy were found amongst patients with anaplastic tumours, but apart from the single nodule it did not appear that the type of local tumour had any influence over the outcome of therapy, though the size of the series is small.

Review of those patients who developed metastases following irradiation in respect of the time interval between treatment and appearance of metastases suggests that a substantial number harboured occult metastases in bone or regional lymph nodes at the time of original assessment.

If it should prove possible to detect such occult metastases then the results of irradiation treatment in a more select group should be very much improved. Present diagnostic methods are inadequate for reliable detection of such metastases.

Protocol for Irradiation in the Management of Prostatic Carcinoma

By P. JULIAN METZNER, FRCS, FRCSE, FRACS
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During 1974 in Australia, it is anticipated that approximately 1,200 new cases of carcinoma of the prostate will be clinically diagnosed and pathologically confirmed. Carcinoma of the prostate is second only to carcinoma of the lung in the adult male population and has a calculated incidence of 80 cases per 100,000 males over the age of 35 years. This figure is considered to be low and the actual figure is thought to more closely approximate the American figure of 120 cases per 100,000 males over 35 years.

Beneficial results have been observed using Mega voltage deep X-ray therapy (MeV DXRT) in a small group of patients suffering from carcinoma of the prostate whose clinical condition was considered to be terminal. The most encouraging aspect of their response was the immediate local regression of tumour with apparent continued control and regression in the follow-up period.

A review of world literature indicates that MeV DXRT for carcinoma of the prostate dates only from 1965 and though there is as yet insufficient information regarding the long-term effects, initial reports are all encouraging.

Complications resulting from MeV DXRT appear to be minimal and with much reduced morbidity in comparison with other methods of treatment.

Because of the confusion that exists in the evaluation of all forms of therapy for carcinoma of the prostate and the apparent difficulty of obtaining significant numbers in any one area, it is proposed that a National Co-operative Study be initiated under the auspices of the Urological Society of Australasia. An attempt will be made to set up a National Registry to determine the results of current forms of therapy and hopefully to provide an indication of the optimum form of therapy for this condition.

The Radiographic and Cystoscopic Classification and Natural History of Vesico-ureteral Reflux

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Vesico-ureteric reflux is present in a third of children with urinary infection and is the major cause of chronic pyelonephritis in children and adults. The aim of this study was to determine the indications for surgery related to the severity of reflux at presentation.

Observations were made upon 1,000 children with primary reflux. Of 1,518 ureters, 28% had gross reflux which distended the renal pelvis, 63% had moderate reflux which filled the renal pelvis and 19% had slight reflux which filled the ureter alone.

Follow-up observations were made for a period of 5 years or until the reflux ceased. Cessation occurred in 509 ureters. Gross reflux ceased in 30% of ureters, the rate decreasing from 50% in infants presenting under 1 year of age to 11% in children over 10 years.

Moderate reflux ceased in 75% of ureters, the rate decreasing from 95% in infants to 63% in adolescents. Reflux in older children ceased in 88% of ureters associated with normal kidneys and in 44% of those with scarred kidneys. Slight reflux ceased in 91% of ureters.

Of 340 children with renal disease, 317 (93%) had scars at presentation. Scars developed in 45% of normal kidneys associated with gross reflux and in 1-2% of kidneys with moderate or slight reflux. At the conclusion of the study renal disease was found in 79% of ureters with gross reflux, in 11% of those with moderate reflux and 12% of those with slight reflux.

X-ray findings were compared with cystoscopic grading of the ureteric orifice in 160 children. The severity of reflux and incidence of scars increased with laterality of the ureteric orifice. The length of the submucosal tunnel was less than 5 mm in 20% of ureters with moderate reflux. These ureters probably constitute those that will not cease spontaneously.

The conclusions from this study were that:

1. The classification of reflux into gross, moderate and slight categories correlates well with the natural history of the disease.
2. Surgery is indicated in ureters with gross reflux and those with moderate reflux associated with renal scarring.
3. Conservative treatment with intermittent or maintenance chemotherapy is indicated in most ureters with moderate or slight reflux. Cystoscopy will help identify the ureters with a short submucosal tunnel and little chance of spontaneous cessation.

The Effect on Renal Growth of Re-implantation of Refluxing Ureters

By C. U. McRae, FRCS, FRACS
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Although it has been clearly shown that surgery is successful in stopping reflux in 80-90% of operations on ureters with varying degrees of reflux, there is little information about the effects of stopping reflux on the kidney above. 39 children have been reviewed with emphasis upon the effect which primary re-implantation of ureters with gross reflux might have had on subsequent episodes of bacteriuria and upon renal growth as assessed by measurements of kidneys on repeated intravenous pyelograms.

All kidneys drained by ureters without vesico-ureteric reflux grew at a normal rate; 10 out of 12 ureters with moderate reflux had kidneys with normal growth rate regardless of re-implantation surgery.

45 ureters with gross pre-operative reflux were assessed for both postoperative reflux and renal growth. There was a significant association ($P = 0{\cdot}01$) between the absence of postoperative reflux and normal renal growth. There was no association between the incidence of postoperative episodes of bacteriuria and normal renal growth. When gross reflux persisted postoperatively, a normal growth rate was not observed in any kidney.

It is therefore suggested that only kidneys with grossly refluxing ureters are at risk and it has been shown that lesser degrees of reflux allow for normal renal growth to occur irrespective of ureteric re-implantation. However, surgical correction of gross vesico-ureteric reflux is indicated because in preventing further reflux, it may lead to a resumption of normal renal growth.

Vesico-ureteral Reflux

By R. B. Brown, FRCS, FRACS
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The incidence of vesico-ureteral reflux was found to be high (22%) in female children presenting with recurrent urinary tract infection and in female adults with recurrent infections and pyelographic evidence of pyelonephritis (44%). It is considered that patients with primary low pressure reflux to the kidney, recurrent infections and gaping, lateral, short submucosal ureteric length required surgical correction of the abnormality provided that the ureters were not grossly dilated and that renal failure was not present. Renal failure, mega-ureter, minimal and secondary reflux were considered to contraindicate surgical treatment of reflux.

A series of 52 anti-reflux operations have been carried out in 36 patients; 46 of these procedures used the Leadbetter-Politano technique and with 6 the Paquin technique and the procedure was combined with Y-V plasty to the bladder neck in 2 patients and with resection of posterior urethral valves in 1 patient. During a follow-up period of at least 2 years surgical treatment of reflux was successful in 78% of patients in the first half of the series and in 90% of patients in the second half of the series. Success was defined as cessation of reflux with maintenance at least of the preoperative total renal function, postoperative freedom from urinary infection and cessation of preoperative symptoms.

Of the 7 unsuccessful operations, 2 were associated with mega-ureter, 1 with extravesical postoperative ureteric obstruction with kinking which could have been avoided by extravesical mobilisation of the ureter.

72% of the kidneys drained by refluxing ureters subjected to surgical treatment were regarded as pathological prior to the operation. Postoperative assessment showed that 26% of these kidneys improved their function and/or growth rate whilst the other successful cases maintained their preoperative status. Progress of renal scarring was not noted in any of the operative successes.

During the 2-year period of follow-up 9 patients presented with urinary infection on routine monthly testing. Surgical treatment of the vesico-ureteral reflux had been successful in 5 of these patients whilst in the remaining 4 patients obstruction and/or continued reflux had obtained. If the anti-reflux operation had been technically successful then postoperative bacteriuria did not appear to be associated with further renal damage.

Impotence and Urethral Stricture

By R. M. Chambers, FRCS
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Impotence is a common and serious accompaniment of urethral stricture in the male population of Uganda.

It is often associated with reflux of urine into ducts or cavities in the prostate and adequate relief of the urinary obstruction by dilatation or surgery is often followed by improvement in potency.

In New Zealand few patients with impotence have demonstrable penile or perineal urethral stricture. Many of these patients have symptoms of prostatitis or bladder irritability and some may show reflux into prostatic ducts. Similarly, many patients with non-infective prostatitis also have difficulty with potency. Most of these patients with impotence or with prostatitis have an obstructing urethral lesion which is most commonly found at or just inside the external urethral meatus. Relief of this obstruction is often followed by improvement of symptoms due to prostatitis and of sexual potency.

120 Infertile Men

By WARREN JOHNSON, FRACS
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In a series of 120 men presenting with infertility the underlying cause was thought to be varicocoele in 38, testicular failure in 30, duct obstruction in 10, cryptorchidism in 3, endocrine disturbance in 3, seminal viscosity in 1, seminal volume in 1 and was unknown in 34 patients.

18 patients with large varicocoeles and poor semen quality were treated by a high ligation procedure with 5 subsequent pregnancies. There were 6 pregnancies associated with 20 untreated patients with small varicocoeles and only slightly impaired semen quality. The precise role of varicocoele in infertility remains unclear, but experience with individual cases does suggest that ligation may have a very marked beneficial result.

Azoospermia was found in 34 patients and was attributed to duct obstruction in 8, primary testicular failure in 6, cyclophosphamide medication in 6, Sertoli cell only syndrome in 4, varicocoele with testicular failure in 3, congenital absence of the vas deferens in 2, hypogonadal hypopituitarism in 1, Klinefelter's syndrome in 1, undescended testis in 1 and the cause was unknown in 2 patients.

Vasoepididymostomy was carried out in 5 patients but only a few sperms appeared in the ejaculate of 1 of these patients and there were no pregnancies in this small group.

Cyclophosphamide treatment of chronic glomerulonephritis can sterilise both men and women. In the male, testicular biopsies showed complete or almost complete absence of germinal cells, but these changes were found to be potentially reversible after cessation of therapy. HCG has been used successfully in the treatment of idiopathic infertility with low sperm motility. Improvement was noted after such treatment in 14 of a group of 21 patients and there were 8 subsequent pregnancies.

Coitus interruptus has been recommended for 3 patients with high semen volume and low sperm density and for 1 otherwise oligospermic patient with a normal first fraction when the ejaculate was partitioned by collection in 2 containers. 2 pregnancies have followed this treatment in a group of 4 patients.

In the entire series of 120 patients 31 men have been successful in producing at least 1 pregnancy and 14 of these 31 received specific treatment.

The Polomo Operation for Varicocoele and its Effects on Fertility

By DAVID GUNTER, FRACS
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Treatment of infertility in 60 men with varicocoele has been applied by the Polomo technique of ligation of the testicular vessels, artery and veins on the posterior abdominal wall above the level of the deep inguinal ring. In each of the patients repeated seminal analysis was carried out for a preoperative period of at least 2 months. The patients were encouraged to change out of supportive underwear. Most of them were given supplementary Vitamin E, were prescribed adequate rest and spaced intercourse to coincide with ovulation times. Any uro-genital infection was treated where necessary. In each of the 60 patients bilateral operations for varicocoele were carried out and in 19 patients testicular biopsy was also performed. At operation the testicular vessels were exposed extraperitoneally through a MacBurney type incision but with splitting of the internal oblique muscle at a high level to avoid interference with the shutter mechanism of the internal oblique muscle in the inguinal canal and to obviate the risk of a postoperative development of inguinal hernia.

In follow-up it was thought that after operation the 60 men were responsible for 31 pregnancies to provide an overall conception rate of 52%. In those patients subjected to testicular biopsy 1 pregnancy was associated with normal testicular tissue as found in 2 patients, 2 pregnancies in 3 patients with mild or moderate hypospermatogenesis, 4 pregnancies in 8 patients with moderately severe hypospermatogenesis, 2 pregnancies in 3 patients with Sertoli cell only syndrome and no pregnancies followed operation in 3 patients with doubtful findings on testicular biopsy.

In 38 of the 60 men pre- and postoperative seminal analyses were compared. The sperm count improved in 63%, sperm mobility improved in 53% and sperm morphology improved in 40%.

17 pregnancies occurred in a group of 29 of the 60 patients who showed increase in testicular size on one or both sides after varicocoele surgery. 14 pregnancies occurred in 31 patients without detectable difference in testicular size; in no patient was the varicocoele surgery associated with decrease in size of testis.

Evaluation of a Technique of Kidney Cooling in Partial Nephrectomy

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Cooling of the kidney has been effected by submerging the mobilised kidney with clamped renal artery and vein in chilled normal saline and saline slush contained in a sterile plastic bag. The bag is the same type used to enclose exenterated bowel, but a hole is cut in the bottom of the bag which is then inverted and placed over the kidney and the tapes are then tightened so that the normal top of the bag fits snugly around the renal pedicle.

The cooling mixture is prepared by mixing equal quantities of iced saline and normal saline at room temperature; during cooling fluid is repeatedly added to the bag to prevent constant contact of ice with the kidney surface.

The changes in kidney temperature are measured by an electric thermometer probe which is inserted to a depth of 2 cm into the renal substance. A very predictable fall of temperature of 20°C is usually obtained after 10 minutes of immersion and the temperature remains within 3°C of this level for 30 minutes and then begins to rise more rapidly.

This technique has been used in 14 cases of partial nephrectomy; in each case the technique was swift to perform and took less than 3 minutes to establish; renal temperature rapidly returned to normal after release of the vascular clamps at the end of the procedure. Radiological evaluation was performed in each case some 6 months after operation and no deterioration of function in the remaining renal tissue was defined. Stone-bearing patients showed no recurrence of calculus and all patients were normotensive and without urinary infection.

Uretero-ureteral Anastomosis in the Surgery of Duplex Ureters

By R. Fowler, MD, FRACS

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The place of uretero-ureterostomy in current urological practice is still uncertain. Conversion of double ureteric drainage to a "high-Y" bifid system, either by uretero-ureterostomy or pyelo-ureterostomy, has previously been advocated in the treatment of ureteral ectopia or of reflux up only 1 ureter in a pair. The procedure is probably least justified in either of these contexts, in which the technical problems are maximal and for which more satisfactory surgical alternatives are available. However, in the surgical treatment of conjoined ureters, uretero-ureteral anastomosis merits further consideration as an alternative to heminephrectomy.

Though conjoined ureters do not always present surgical problems, and some may remain trouble free for years, they all display a degree of stasis and susceptibility to infection because of uretero-ureteral reflux. Indications for surgery include uncontrolled infection, congenital stenosis and apparent functional obstruction or "dyskinesia".

Of 12 uretero-ureteral anastomoses performed in 10 children, stenosis was encountered as a complication in only 1 patient in whom a partial stenosis developed after pyelo-ureterostomy for correction of orthotopic reflux in a complete duplex system. No anastomotic complications were encountered in 9 "high-Y" conversions undertaken for conjoined ureter problems presenting as stenosis in 1 patient, dyskinesia in another and as infection in 7 patients. In these 7 children, "high-Y" conversion was a major factor in elimination of infection. These results are considered in relation to alternative methods of management, both operative and non-operative, employed in a total of 24 conjoined ureters in 23 children.

From the satisfactory results obtained, uretero-ureteral anastomosis emerges as a thoroughly acceptable procedure, with a definite place in present day urological practice, and chiefly in its application to the problem of conjoined ureters rather than complete duplication.

Urethral Obstructions in Children

By F. Douglas Stephens, DSO, MS, FRACS

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140 intrinsic obstructions of the urinary outflow tract (excluding overt neurogenic lesions and external meatal stenosis) were observed during the past 20 years at the Royal Children's Hospital. These were chiefly located in the posterior urethra of boys.

Two lesions, usually known as Young's valves, types I and III were responsible for approximately 80% of the intrinsic urethral obstructions. Type I valves were the more common and were sagittally arranged hypertrophic folds arising from the verumontanum or inferior crest coursing distally to meet on the anterior wall of the urethra. Type III valves in this series were short mucosal strictures or circumferentially attached membranes in the vicinity of the membranous urethra or adjoining part of the bulbous urethra. The perforated membranes were transverse or cupped distally or lying redundant in the lumen like a sock. Other causes of urethral obstruction included urethral and occasionally vesical diverticula (10) ureteroceles (approximately 10) and polyps of the verumontanum (7).

The urinary tract of patients with urethral valves may exhibit vesical diverticula, vesico-ureteral reflux (42% of patients and 28% of the renal units), gross dilation of the ureters and hydronephrosis (76% of patients) or renal deformities including duplication, cysts, or absence.

In the boys with Young's valves, the mortality rate from infection and renal failure at the time of first admission was 25% in the first 10 years of the survey but during the past 10 years, following the introduction of improved urinary drainage only 6 such patients have died. Most of the valves were treated by endoscopic resection or diathermy. 74 patients were followed for an average period of 5·4 years; 6 developed renal failure, 2 died and 1 had a successful renal transplantation.

Vesicoureteral reflux was found in 28% of evaluated ureters. Spontaneous cessation occurred after removal of urethral obstruction in 14% of ureters, but 5 ureters required re-implantation to prevent persistent reflux. In addition, 9 patients had re-implantation operations for suspected additional uretero-vesical obstruction and 3 patients required pyeloplasty to relieve pelvi-ureteric lesions. No permanent urinary diversions were performed.

The Non-neurological Uninhibited Bladder

By E. P. Arnold, FRCS

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An uninhibited or unstable bladder is characterised by the occurrence of involuntary detrusor contractions which the patient is unable to inhibit. It signifies an over-excitable micturition reflex which may occur as a result of a reduction of the overall inhibitory effect of descending cerebrospinal pathways in neurological disorders, but also frequently occurs in the absence of detectable neurological lesions in patients with bladder outlet obstruction, enuresis, in many women with urinary incontinence, and in many patients—both men and women—with symptoms of frequency, nocturia, urgency or urge incontinence.

The uninhibited detrusor can be detected by supine cystometry, but the additional provocative tests of passive change of posture from supine to erect, and of coughing will allow the detection of many more patients who have detrusor instability causing symptoms.

The importance of detecting detrusor instability lies in the poor results of operations for incontinence in women when abnormal detrusor function is present. As instability is associated sometimes with symptoms mimicking those due to bladder outlet obstruction, it is important to obtain objective evidence of obstruction when a patient has the symptoms of frequency, nocturia, poor stream, together with urgency and urge incontinence, since prostatectomy in the non-obstructed group is likely to aggravate the symptoms by reducing the outlet resistance.

The management of the non-neurological unstable bladder is far from simple. Correction of outlet obstruction when associated with detrusor instability will lead to a return of stable bladder function in most cases, but where instability is due to other unidentifiable causes, drug therapy with antispasmodics is worth trying. The place of adrenergic drugs alone or in combination with progesterone or oestrogen deserves further evaluation.

Operations designed to denervate the bladder are successful sometimes, but early success is often marred by late failure. Where routine operative measures have failed and when urodynamic studies indicate adequate sphincter function, caeco-cystoplasty deserves consideration as an alternative procedure to urinary diversion in patients who are incapacitated by urinary incontinence due to detrusor instability.

Treatment of Renal Trauma by Angiographic Injection of Autologous Clot

By SHERMAN JAY SILBER, MD

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Persistent haemorrhage from blunt renal trauma, with hypotension, falling haematocrit or expanding flank mass, is generally treated by surgical intervention. The first report of an alternative and perhaps preferable treatment, is presented.

A 15-year-old boy was admitted with a 1 hour history of total gross haematuria and left flank pain and tenderness, following blunt renal trauma. Admission pyelogram showed delayed function from the left kidney with blood clot in the collecting system and slight peri-ureteral extravasation. During the next 9 days of conservative management with bed rest, he continued to have gross haematuria with flank pain and required a transfusion with 4 units of blood. Further pyelography showed no improvement in the left kidney and selective renal arteriography showed several areas of bleeding from branches of the superior segmental portion of the lower of 2 renal arteries. 0·7 ml of fresh clot from the patient's own blood was injected into this branch and created total occlusion of the superior segmental branch with cessation of bleeding and immediate clearing of the urine. Repeated selective arteriography after 5 days and at 3 months demonstrated a completely cleared, open, unoccluded renal arterial tree with only a tiny area (less than 5%) of infarction.

Experimental studies in rats by injection of relatively huge volumes of autologous clot into the renal arterial circulation revealed the same remarkable clearing phenomenon by endogenous fibrinolytic activity, and indicated a wide margin for safety in the clinical use of this technique in patients with renal bleeding.

The Urological Case Histories of Nicolas Tulp

By LEONARD J. T. MURPHY, MD, MS, FRACS, FACS

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Nicolas Tulp of Amsterdam (1593-1616) has achieved immortality as the subject of Rembrandt's "Anatomy of Nicolas Tulp" but is less well known as a leading physician and the author of *Observationes Medicae.* This book, first published in 1641, contains in the enlarged edition of 1652, over 200 chapters among which are found the first descriptions of the ileo-caecal valve and very early accounts of beriberi and many other subjects.

His urological cases are too numerous to consider in detail. Among renal calculi reported are bilateral stag-horn calculi and a stone extruded through the skin of the loin, followed by a urinary fistula. He uses these cases to assert that the suggested surgical removal of renal calculi would be of no benefit even if technically possible. A patient who died of anuria due to calculi impacted in both pelvi-ureteric junctions is regarded as beyond medical aid.

An extraordinary case is that of the clergyman who developed anuria whenever the moon was almost full. At postmortem, a hydronephrotic kidney and 2 vesical calculi were found but hardly explained his odd syndrome.

Vesical calculi are discussed, with repeated warnings of the dangers of lithotomists attempting to remove stones in diverticula. One female patient passed 300 calculi in one burst and another expelled a calculus weighing over 3 ounces without medical aid. "Worms" in the urine, resembling mites, ascarides and odd insects, were almost certainly contaminants. He also relates the famous case of Jan de Doot who removed a subcutaneous calculus from his perineum with a kitchen knife.

Other items include a very early account of Peyronie's Disease, and reports of hypospadias, hermaphroditism, an infant with an imperforate anus who passed both urine and faeces through a hypospadiac meatus, and a large urethral diverticulum full of calculi.

Two cases of bladder injury were followed by foreign bodies in the bladder: in 1, a large fragment of pubic bone was found at postmortem and, in the other, a stone formed round a stent lost in the bladder during treatment of a penetrating wound. One remarkable case of the intermittent passage of hairs embedded in lumps of mucus per urethram suggests a dermoid cyst opening into the bladder. Tulp is reported to have provided the first clear description of carcinoma of the bladder but chronic infective changes round the rectovesical fistula resulting from lithotomy many years previously could have caused such changes as he described.

Tulp lists incision, hook and suction as methods of removing urethral calculi and, except for those adjacent to the meatus, advises the Egyptian method of distending the urethra with air and manipulating the stone forwards.

Tulp's clinical observations, accompanied by post-mortem findings, make his book a treasure-trove of interesting urological cases, though few patients, apart from those requiring lithotomy or some minor surgery, would have derived much benefit from the treatment available at the time.

Management of Late Stage Carcinoma of the Bladder

By H. THOMAS, FRCS, FRACS, FACS

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The results achieved by radiotherapy in the treatment of bladder carcinoma at The Prince Henry, Prince of Wales and Eastern Suburbs Hospitals Group have been reviewed over a 5-year period from 1967-72. 66 cases were studied and of these the clinical classification gave 2 T1, 35 T2, 17 T3 and 12 T4 staging. Pathological grading of the tumours was based upon the degree of anaplasia of the cells and 1 case was classified as Grade I, 25 cases as Grade II and 40 as Grade III. At the time of cystoscopy tumours were biopsied or endoscopically resected according to the extent of the tumour.

The age scatter of the cases showed a major presentation in the 60-79 year group. Haematuria was the major presenting symptom and it occurred much earlier in the Grade III cases than in the Grade II. There was a predominant incidence of single tumours in both males and females.

Results were assessed on a percentage basis according to the tumour stage and it was found that T2 tumours had an apparent cure rate of 42% and a recurrence control rate of 35% whilst 23% were uncontrolled or died from tumour. In the T3 group 16% showed apparent cure, 20% had recurrence controlled and 64% were uncontrolled or died from tumour. The T4 group showed 5% apparent cure and 95% mortality. It was thought that the rather high rate of recurrence, both controlled and uncontrolled, in the T2 cases was a reflection upon the inaccuracy of clinical staging.

Results in respect of histological grading showed that Grade II cases had an apparent cure rate of 30% with 26% of patients having recurrence controlled and 44% with uncontrolled recurrence or death. The Grade III cases showed 34% without recurrence, 21% with recurrence controlled and 45% with uncontrolled recurrence or death from tumour. The morbidity after radiotherapy showed that a surprisingly small number of cases had no symptoms even with apparent cure.

Treatment of recurrence after radiotherapy consisted of repeated diathermy or localised resection in 13 patients, total cystectomy in 9 patients whilst the remainder received symptomatic treatment.

It was considered that in comparison with reported results of preoperative radiotherapy followed by cystectomy for bladder cancer, these present results were not as satisfactory in relation to the T3 cases; for such tumours a combination of radiotherapy and cystectomy offers a better chance of cure and is recommended.

A Simple Aid to Urinary Cytology

By L. I. PARTON, MB, BSC, FRCS

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New Zealand

In 2 cases an epithelial tumour of the upper urinary tract was suspected but repeated urinary cytology was negative. In 1 case a positive result was then obtained by passing a ureteric catheter to the renal pelvis, washing it out with saline and examining the washings. In the other case a positive diagnosis was obtained by using a Dormia stone basket to obtain a small piece of tumour. It is felt that such extremely simple and logical measures have not received enough emphasis in the literature. Gill, Lu and Thomsen (1973) however, have described a somewhat similar method using a small brush as applied to gastroscopy and bronchoscopy. In the absence of this more sophisticated equipment, the simpler methods described may prove a very helpful aid in cytology and will increase the chances of obtaining a positive result.

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A Bacteriological and Clinical Assessment of a New Drug—Oxolinic Acid

By MALCOLM DRUMMOND, FRACS

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Oxolinic acid is a new drug developed for the treatment of urinary tract infection. In-patient organism sensitivity has been studied and in comparison to the other commonly used antibiotics it can be seen that the coliforms are highly sensitive to this drug. *Pseudomonas aeruginosa* has been recognised as being universally resistant to the drug and sensitivities have not been performed.

The chemical structure of nalidixic acid and oxolinic acid is similar and there is a high degree of correlation between organism sensitivity to nalidixic and oxolinic acids. The drug is readily absorbed from the gastrointestinal tract and the mode of action is upon DNA synthesis. A low serum concentration of the drug has been reported after 7 days' treatment while the urine concentration is high at 15-155 μg/ml. This concentration is many times higher than the minimum inhibitory concentration of 1 μg/ml.

Studies were carried out upon 50 patients in hospital with established urinary tract infections.

Their ages ranged from 15-80 years and the group were comprised of 11 female and 39 male patients and most of them had persistent or recurrent urinary tract infections. Cultures prior to treatment were carried out upon urine samples obtained as midstream specimens, catheter specimens or at cystoscopy. The drug was given in a dose of 750 mg twice daily for 7 days and a follow-up urine examination was performed 10 days after commencement of treatment.

21 *Klebsiella* infections were treated and 6 were eradicated and 15 persisted; 19 *E. coli* infections were treated and 14 were eradicated and 5 persisted; 6 *Proteus* infections were treated and 5 were eradicated and 1 persisted; 2 *Staph. albus* infections were treated and 1 was eradicated and 1 persisted; 2 *Strept. fecalis* infections were treated and 1 was eradicated and 1 persisted; 1 mixed infection with *Klebsiella* and *Proteus* was treated but remained infected.

Overall there was successful eradication of sensitive organisms in 50% of infections. In 4% of the infections the original organism persisted and remained sensitive. In 28% of infections the organism developed drug resistance during the course of treatment.

In respect of classification of organisms it was found that 50% of *Klebsiella* infections which were initially sensitive to the drug developed resistance during treatment, whereas only 10% of *E. coli* infections developed resistance. The difference was found to be statistically significant ($P = 0{\cdot}01$).

It would appear that oxolinic acid should be an extremely useful drug because of the high initial sensitivity of coliform organisms, the advantage of twice daily dosage and the high urinary concentration exceeding the minimum inhibitory concentration. However, in this series, there was an unacceptably high rate of emergence of resistant strains of organisms during the treatment of *Klebsiella* infection for which this drug could no longer be recommended. A similar rapid development of resistant strains has also been reported during treatment with nalidixic acid and this may relate to similarity in a chemical structure between nalidixic and oxolinic acids.

Various Uses for the Storz Nephroscope

By B. S. PEARSON, FRACS

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The Storz nephroscope was designed to inspect the interior of the renal pelvis and calyces but it has been found useful in the diagnosis of lesions of the kidney, ureter, bladder and urethra.

Radiotranslucent deformities of the renal pelvis and calyces have been inspected through an incision in the pelvis, surrounded by a pursestring suture to prevent spillage. This technique allows for diagnosis and biopsy of tumours with diathermy coagulation of non-invasive tumours under special conditions. The nephroscope may be of use in the evaluation of essential haematuria with the avoidance of nephrectomy. The instrument allows for the inspection of intrarenal cysts and calyceal diverticula for the exclusion of malignancy whilst individual calyces may be inspected to clarify the need for partial nephrectomy or to assist in water-tight closure of the calyx at this operation. Calculi may be located and removed through the nephroscope by accurate manipulation of biopsy forceps with controlled local irrigation and sometimes combined with cooling for the more complete eradication of staghorn calculus.

Endoscopic inspection of the dilated ureter is possible through ureterotomy controlled by pursestring suture with access for biopsy or fragmentation of calculi.

The nephroscope may be useful for the internal inspection of bladder diverticula or viewing of the prostatic urethra from above. The instrument might also be of assistance in high and difficult urethroplasties as it provides a light source with easy irrigation to clear bleeding and with optical magnification.

During the past 2 years the nephroscope has aided the surgical management of renal calculi on 30 occasions, the diagnosis of intrarenal filling defects on 4 occasions, the diagnosis and management of lesions in the ureter on 3 occasions and the management of bladder deiverticulum on 1 occasion.

Urinary Diversion in Carcinoma of the Cervix: A Report of 40 Cases

By D. R. H. KENNEDY, FRCS, FRACS

Royal Women's Hospital, Melbourne, Victoria

During a 7-year period from 1956 urinary diversion was carried out upon a series of 40 patients with carcinoma of the cervix uteri.

Urinary diversion was indicated for palliation of malignant vesico-vaginal fistula (10 patients), as a preliminary to radiotherapy in advanced cases with bladder involvement and a high risk of fistula formation after therapy (18 patients), and with the complications of primary treatment of the carcinoma. These complications included bladder denervation after Wertheim hysterectomy (5 patients) with progressive hydronephrosis, gross bladder trabeculation and poor urinary control. Combination of radiotherapy and surgery was sometimes complicated by anuria, ureteric stricture, fistula, radiation cystitis and urethral damage. The average radiation dose was between 4000 and 7200 r.

In 4 patients ureterostomy was performed as a palliative procedure and in each of these patients complications developed in association with stomal stricture. In 1 patient a rectal bladder was fashioned with colostomy but this was later converted into ileal conduit diversion because of rectal urinary incontinence.

In the remaining 36 patients ileal loop diversion was used and has been the method of choice since 1967.

Complications following ileal conduit diversion were more common amongst 20 patients who had received preoperative radiotherapy. There were 3 postoperative deaths, 1 due to urinary leakage, 1 with dehiscence of the ileo-ileal anastomosis and the third death followed laparotomy for postoperative intestinal obstruction. A fourth patient developed bilateral renal calculi and died from septicaemia after ureterolithotomy 7 years after diversion. In 1 patient refashioning of a new loop was required because of ileal gangrene. 4 patients developed persistent paralytic ileus and 4 patients developed urinary fistula and 4 patients had wound infection but these complications settled after conservative therapy. Pyocystitis was troublesome in 1 patient who died from a coronary occlusion 2 years after diversion.

In the entire group electrolyte disturbance or stomal problems did not occur.

Following 41 urinary diversion procedures carried out in 40 patients with cancer of the cervix, 14 patients are alive and well with normal intravenous pyelograms; 2 of these patients had stage IV tumours and are well 4 years after diversion and postoperative radiotherapy.

Palliation of symptoms is subjective but review of the series indicates that such palliation is worthwhile and has certainly facilitated nursing care in the terminal stages of cancer of the cervix.

The Siting and Techniques for Stomas in Ileal Conduits in Myelomeningocoele Children

By RUTH V. MAGNUS, FRACS

Royal Children's Hospital, Melbourne, Victoria

In siting an ileal conduit stoma the anterior superior iliac spine, the pubic crest and the umbilicus must be avoided. In children with myelomeningocoele additional problems in siting arise because of the abnormal vertebral column, paralytic deformities of the lower limbs, age and small size of child and the changes with growth.

When scoliosis is present the stoma should be placed on the opposite side of the abdomen to the curvature.

Lordosis is now seldom seen due to correction of hip flexion but when present the stoma should be placed in the upper abdomen to avoid tangential pull on the appliance due to gravity.

Paraplegia from a high spinal lesion causes acute flexion when in the sitting position and a flat surface for the appliance may be difficult to find. Also, apposition of the body surfaces with the collecting bag in between tends to occlude the bag or push it off the flange. Resiting may become necessary as growth continues.

Obesity gives a poor surface on which to fit an appliance and dietetic management from an early age is essential.

A small lower abdomen is sometimes found and the stoma is then sited in the upper abdomen with the expectation that it will be resited in the iliac fossa in later life.

Complications involving the ileal conduit stoma include:

1. Herniation of the bowel beside the stoma. This is prevented by careful suturing of the bowel to the peritoneum.
2. Stenosis of the stoma:
    (*a*) Mucosal level: this is due to ulceration. Ulceration may be reduced by a high fluid intake and meticulous hygiene.
    (*b*) Skin-mucosal stenosis is prevented by the insertion of 2 small skin flaps into the circumference of the stoma.
    (*c*) Peritoneal-serosal stenosis is prevented by the use of a cruciate rather than a circular incision.

Abdominal wall obstruction due to a shelving incision is prevented by holding all layers of the abdominal wall together while the incision is being made.

Bacteriology of Ileal Conduits

By C. U. MCRAE, FRCS, FRACS

Christchurch Hospital, Christchurch,
New Zealand

Although it is recognised that ileal conduits frequently harbour bacteria, the origin, growth patterns and significance of these organisms is uncertain.

A review of 65 patients undergoing ileal conduit urinary diversion showed that 20% of the conduits remained sterile. The majority of the remainder progressed to colonisation by *Pseudomonas* or *Proteus* after varying periods of time. This rise in incidence of these organisms could probably be due to the frequent use of broad spectrum antibiotics which might eradicate the more sensitive organisms. When no antibiotics were used, *Proteus* and *Pseudomonas* did not appear as inhabitants of ileal conduits.

In 8 patients, close study of the bacterial populations of conduits postoperatively, suggested that if ureteric urine is infected preoperatively, then urinary organisms become established in the conduit and normal ileal flora disappear. If ureteric urine is sterile, then one of the resident bacteria in the ileum becomes established with the exclusion of the other organisms.

Fistulae Encountered Postoperatively in 1022 Cases of Uretero-intestinal Anastomosis

By A. RANALD MACKENZIE, CHM, MD, FACS

Memorial Hospital, New York

Between 1945 and 1971 the attending and resident staff in the Urologic Service, performed 1022 operations for uretero-intestinal anastomosis. The mortality rates were 9·3% in a group of 496 cystectomies and ileal conduits, 15·3% in 249 ileal conduits, 14·6% in 150 cystectomies and uretero-sigmoidostomies and 7·1% in 85 ureterosigmoidostomies.

Malignant tumour was the reason for diversion in 98·4% of the cases and usually for cancer of the bladder. X-ray therapy did not greatly increase the incidence of fistula formation.

25 small bowel fistulae were seen—an incidence of 2·4%. They occurred most commonly after exenterative procedures with ileal conduits and carried a mortality rate of 84%. Of 9 patients treated conservatively only 1 survived but 3 of a group of 16 patients who were treated surgically left hospital alive. In 4 patients small bowel fistula was associated with evisceration. Treatment of small bowel fistula by immediate operation is preferred when the complication presents as an intra-abdominal catastrophe or is associated with evisceration or rapid clinical deterioration. It is recommended that the fistulous loop be excised and the anastomotic line is wrapped in omentum. When operation can be delayed it is hoped that a bypass operation can be performed with creation of a double-ended mucous fistula leaving the fistulous loop to drain into the perineum or on to the lower abdominal wall.

Large bowel fistula occurred most commonly after ureterosigmoidostomy and after injury to the rectum at the time of cystectomy. There were 34 large bowel fistulae with an incidence of 3·3% and a mortality rate of 24%. The best results were found after conservative treatment of fistulae from ureterosigmoidostomies and with immediate diverting colostomy for fistulae from rectal lacerations.

Urinary fistulae occurred in 56 patients and were seen after all types of diversion with an incidence of 5·5% and a mortality rate of 5·5%. Distinction could be made between fistulae which developed within 10 days of ileal conduit construction and were considered to be technical failures in contrast to those fistulae which appeared late and were thought to result from ischaemic necrosis. Conservative management was sufficient more often for the former than the latter. If conservative treatment fails then nephrostomy or nephrectomy is recommended. Ureteric reimplantation has at times been successful but this procedure entails greater clinical risk.

Reparative procedures are even less successful and nephrectomy is the safest treatment for urinary fistulae of late development. Fistulae from ureterosigmoidostomies are best treated conservatively but when surgery is required then the most conservative operation *viz.* nephrostomy is the procedure of choice.

Gastrocystoplasty

By C. H. Leong, MBBS(HK), FRCS, FRCSE, FACS
G. B. Ong, OBE, MD, FRCS, FRCSE, FACS, FRACS

Queen Mary Hospital, Hong Kong

The use of the colon, caecum or small intestine for reconstruction of the bladder is not without problems. In our experience with long-term follow up of colocystoplasties, patients are troubled by mucus clot retention and bony rarefaction from hyperchloraemic acidosis. The stomach was thought to be a better alternative because the amount of mucus produced was small and there should not be any chloride absorption.

The procedure was first undertaken experimentally in dogs to elucidate whether it was anatomically feasible, whether the "new bladder" would function, whether there was any deleterious effect upon the upper urinary tract and whether the remaining gastric remnant suffered as a result of persistent perfusion of the pyloric antrum.

There seemed to be no anatomical problems using the pyloric antrum based upon the left gastroepiploic vessels as the vascular pedicle. Long-term follow up of the animals showed that the "bladder" had function and there were no obvious side-effects.

The same procedure was done in 11 humans (8 had complete replacement after total radical cystectomy and 3 augmentation cystoplasty for enlarging contracted T.B. bladder). There was no difficulty in mobilising the pyloric antrum down to the pelvis.

Apart from 3 early postoperative deaths from unrelated causes for the total replacement group, the rest have done very well. Postoperative investigations revealed no electrolyte disturbance. There was no evidence of chloride absorption—instead there was a net positive loss of chloride from the "bladder". The "new bladder" contracts well. Repeated intravenous urogram showed no obvious deleterious effect on the upper urinary tract. This was supported by histology of the kidney. The remaining stomach remnant showed no abnormalities. Repeated gastric acid analysis compared well with preoperative values in all patients including the longest follow up of 3½ years and there was no suggestion of stomal ulceration.

In the augmentation cystoplasty group, the "bladder" volume had considerably enlarged and "bladder" functions have remained good.

The results are encouraging and we feel that the stomach has a definite role in replacement of the bladder.

Colposuspension in the Management of Stress Incontinence

By G. F. Murnaghan, MD, CHM, FRCS

The University of New South Wales, Sydney, N.S.W.

After eradication of proximal urethritis and trigonitis by endoscopic diathermy, simple colposuspension by the retropubic approach (Burch, 1961) has been applied to the management of a group of 20 female patients with stress incontinence.

In 12 of these patients stress incontinence had persisted despite previous application of 38 operations including 17 vaginal pelvic floor repairs, 6 suprapubic slings and suspensions and 15 hysterectomies or other operations such as caesarean section, vesico-vaginal fistula repair and ureteric reimplantation. These 12 patients had borne a total of 26 children and shared 182 years of stress incontinence. During a period of follow-up extending to 46 months and with most patients having been followed for longer than 20 months, 8 of these 12 patients have either complete urinary control or experience slight stress incontinence on rare occasions and declare the result of the colposuspension to be excellent or very good. 2 of the 12 patients obtained significant improvement and the remaining 2 patients obtained recovery of urinary control but with severe relapse of incontinence 1 year after colposuspension.

Six patients presented with stress incontinence not previously treated by surgical procedures and not associated with significant genital prolapse but with previous child-bearing and with concomitant urethral syndrome. 5 of these 6 patients obtained relief of stress incontinence by colposuspension and 1 showed significant improvement with subsequent deterioration in association with pathology in the conus medullaris.

Colposuspension cured 2 nulliparous patients presenting with life long stress incontinence at the ages of 16 and 22 years.

The effectiveness of colposuspension to restore urinary control was evaluated by straining cystography and urethral pressure profiles. Loss of the posterior urethrovesical angle was detected in only 50% of patients in the entire series. Comparison of measurements of effective urethral length and of profile amplitude failed to define any features of profile which were characteristic to stress incontinence with or without previous surgical treatment and in comparison with normal profiles.

Reference

Burch, J. C. (1961). Urethrovaginal fixation to Cooper's ligament for correction of stress incontinence, cystocele and prolapse. *American Journal of Obstetrics and Gynecology*, **81**, 281-290.

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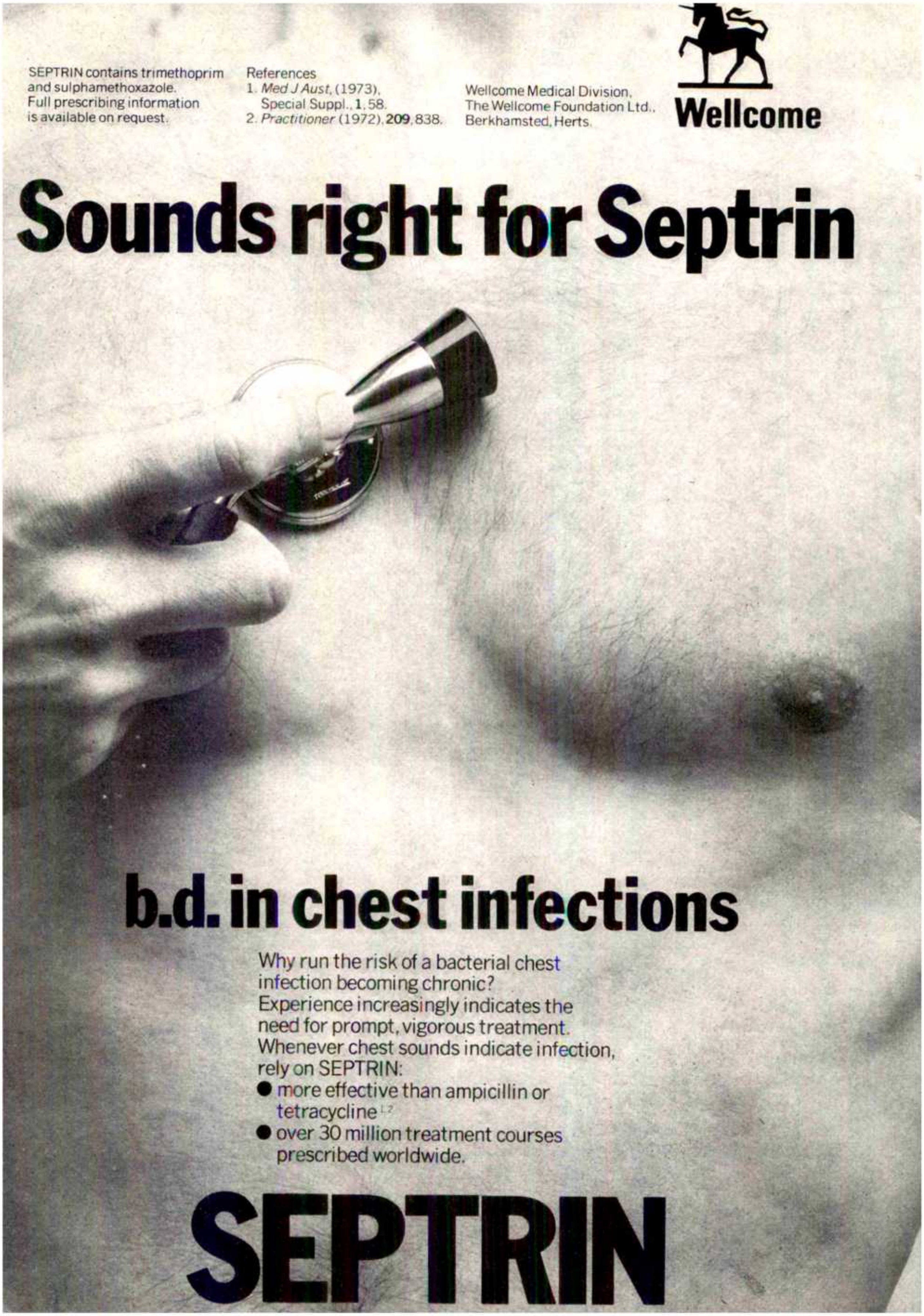

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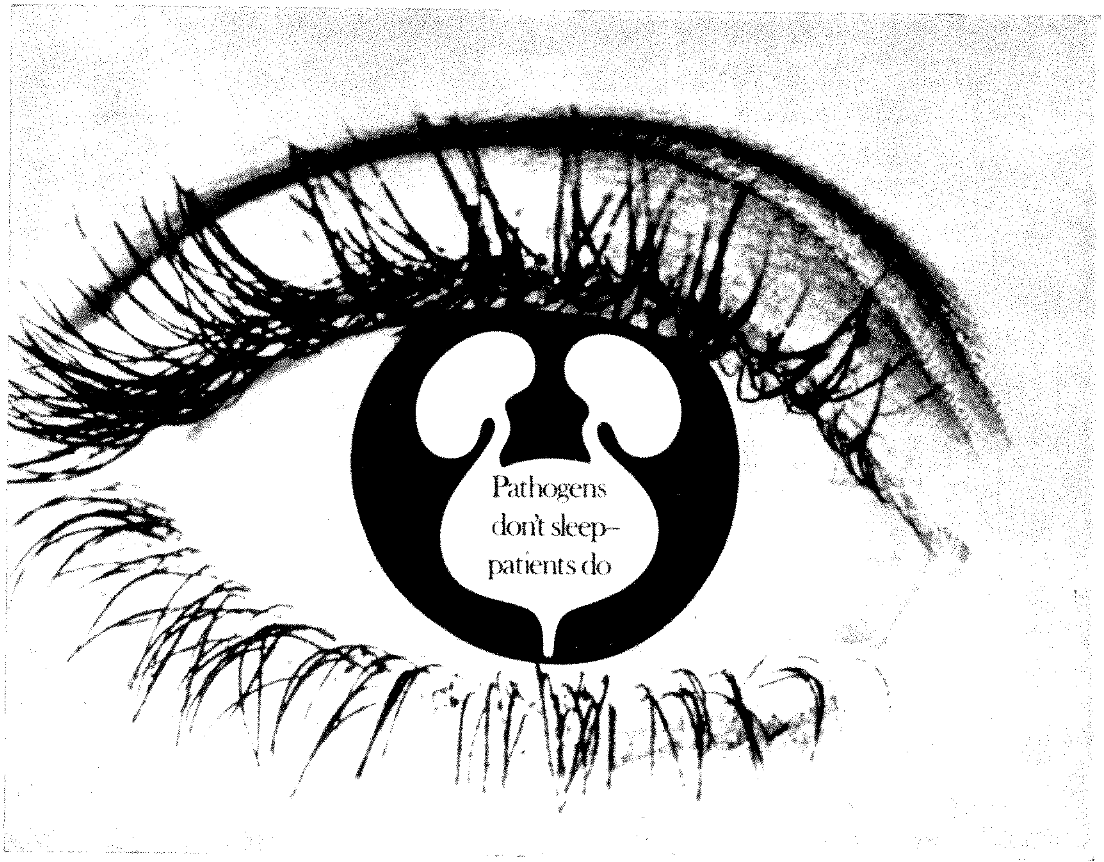

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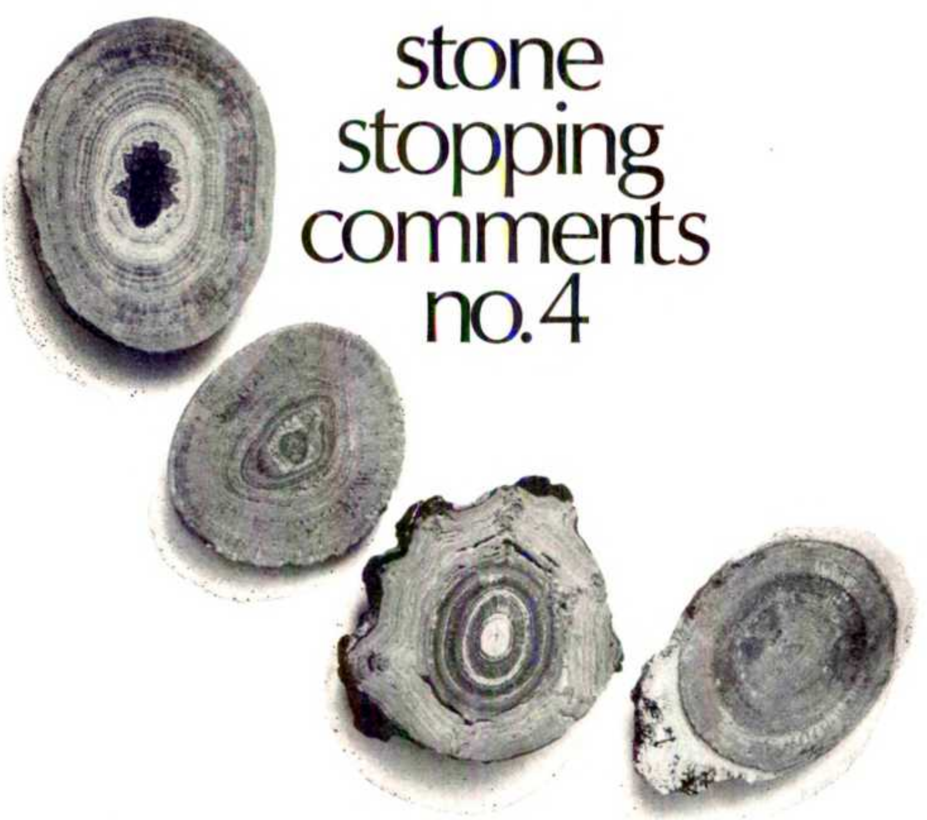

stone stopping comments no.4

In a recent study[1] measurements of ^{47}calcium and of urinary calcium excretion were made in 125 cases of urolithiasis (78 solitary stone, 47 recurrent).

The authors found that 57 out of 60 patients with hypercalciuria showed raised absorption of ^{47}Ca, whereas 49 out of 106 patients showing similar hyperabsorption of calcium had *normal* calcium excretion. The authors concluded that "... a majority of stone formers, whether they are hypercalciuric or not, absorb calcium excessively from the intestine and this is more prevalent in cases of recurrent urolithiasis."

As a sequel to investigation 1, the same authors[2] studied the effect of Sodium Cellulose Phosphate on intestinal calcium uptake. In comparison to a low calcium, low oxalate diet; "Sodium Cellulose Phosphate can significantly diminish the absorption of calcium from the intestine; there is concomitant diminution of urinary calcium excretion. The plasma levels of the divalent cations do not appear to be influenced by this therapy."

Dosage in this study was varied to evaluate therapeutic effect. "Five grams reduced the intestinal calcium by as much as 85% and even a 1 g dose resulted in a 50% reduction ... Such a dose (5 g), however, is probably essential when it is considered that the substance will ordinarily be dispersed throughout a semi-solid food bolus." Optimum administration time was considered to be 5 g t.i.d. at meal times, or within 1 hour after food.
In terms of side-effects and toxicity, the authors stated "Serum levels of calcium and phosphorus were not altered in any of the patients even when the substance had been taken for a period as long as 7 years in a dose of 5 g 3 times daily." There was no diarrhoea or intestinal disturbance, and patients found SCP reasonably palatable and easy to take.

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References
1. Brit J Urol, (1974) **46**: 377-384.
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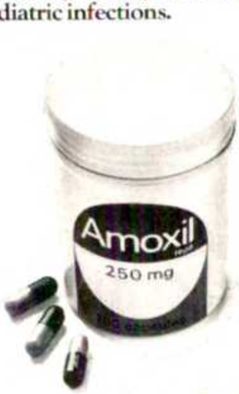

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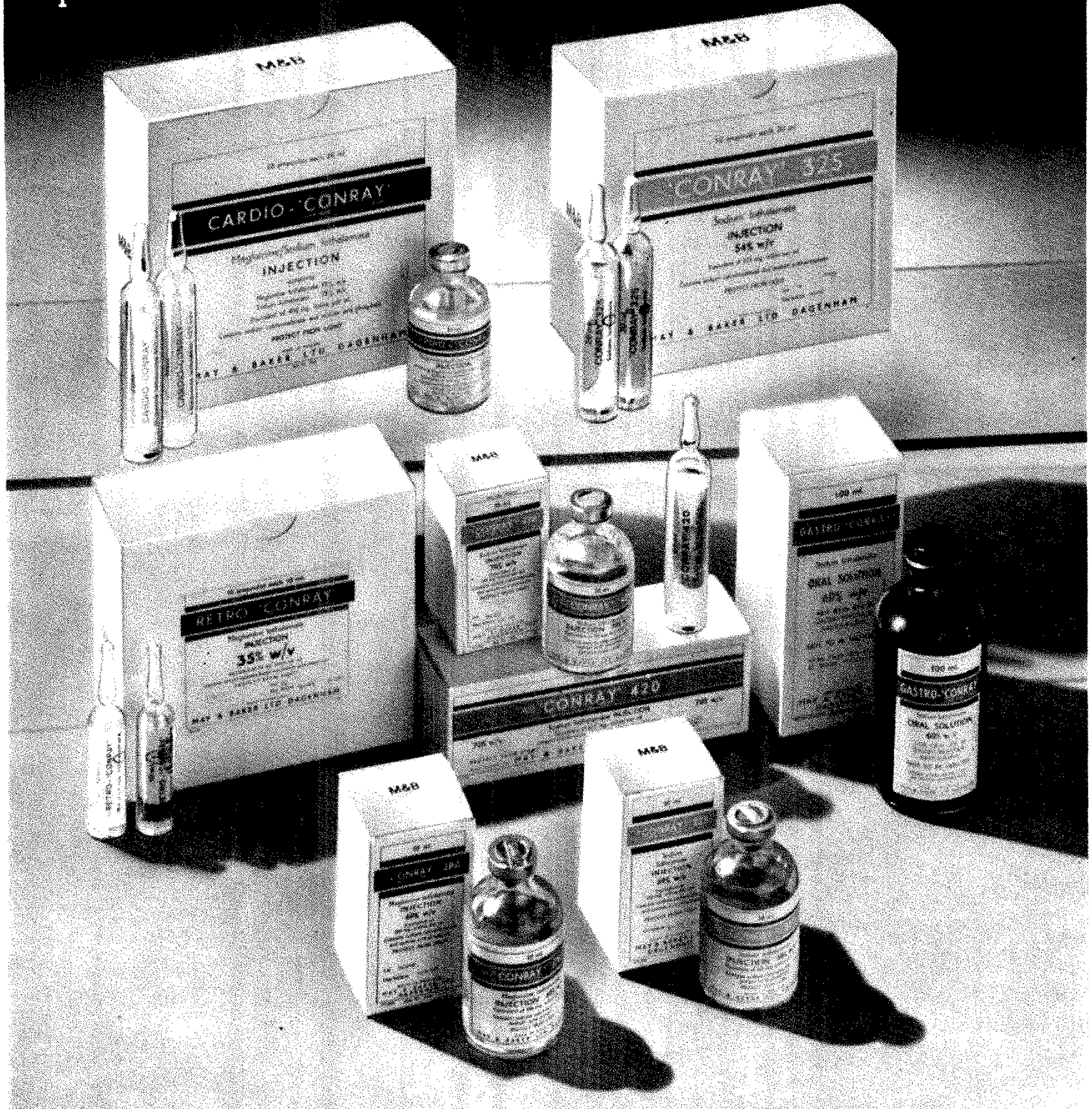

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NORMAL AND ABNORMAL GROWTH OF THE PROSTATE *edited by* **Martin Goland**, *Southwest Foundation for Research and Education, San Antonio, Texas. (90 Contributors)* New and extensive review data are provided concerning comparative embryology and pathology of the prostate. Extensive studies dealing with *in vivo* and *in vitro* prostatic androgen metabolism and the effects of antiandrogens, estrogen and prolactin upon prostatic function are presented. Section I discusses the embryology, development, and pathology of the prostate gland. Included in this section are the fetal and neonatal prostate, the effect of hormones on rat prostatic epithelium in organ culture, structure and pathology of the prostate, rat ventral prostate tissue as a bioindicator for androgen secretion for fetal glands in various species and some morphologic features of normal and pathologic canine prostate. Section II discusses metabolism of steroids in prostatic tissue including control of the concentration and distribution of dihydrotestosterone in prostatic cells. Sections III and IV discuss the regulation of prostatic metabolism. Hormonal regulation of RNA synthesis is reviewed along with biochemical changes in prostatic tissue associated with DNA synthesis. Comments are given on the influence of testosterone on RNA metabolism in the rat ventral prostate. The action of cyproterone acetate on the prostate and heterotransplanted human prostatic adenoma is studied along with the synthetic oestrogens and the prostate, prolactin and the prostate, and zinc in the prostate in man. Section V studies ligand-macromolecular binding and transport mechanisms. Section VI discusses experimental and clinical approaches to prostatic cavity including the effects of chemotherapy on the ventral prostate of the rat and comments on experimental and clinical approaches to cancer of the prostate. This volume will be of value to those directly concerned with problems of prostatic endocrinology and to individuals concerned with the general problem of steroid hormone regulation of target-tissue function. *'75, 964 pp., 451 il., 123 tables, $48.75.*

A HANDBOOK OF URINALYSIS AND URINARY SEDIMENT *by* **Neil A. Kurtzman**, *Univ. of Illinois, Chicago, and* **Philip W. Rogers**, *Brooke Army General Hospital, Fort Sam Houston, Texas.* Common techniques of the clinical examination of urine, their interpretation and the circumstances under which these techniques are of use are discussed. The microscopic examination of the urinary sediment is described in detail accompanied by color illustrations of the more common urinary formed elements. A chapter is devoted to urine in disease in which urinary findings in various renal and metabolic disorders are presented. Emphasis is placed on careful technique and uses and limitations of urinalysis as a diagnostic tool are stressed. This reference source will be valuable to students and physicians. Contents of the book include collection of urine specimens, general considerations, chemical abnormalities of urine, examination of the urinary sediment and the urine in disease. Only those substances deemed to be of prime importance are included. *'74, 112 pp., 28 il. in color, 2 tables, $8.50.*

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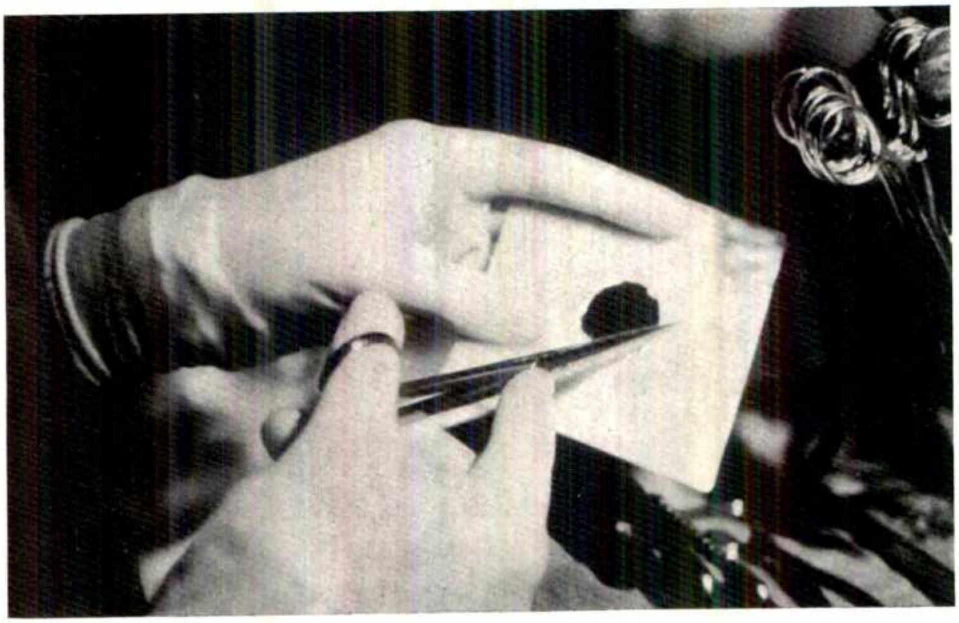

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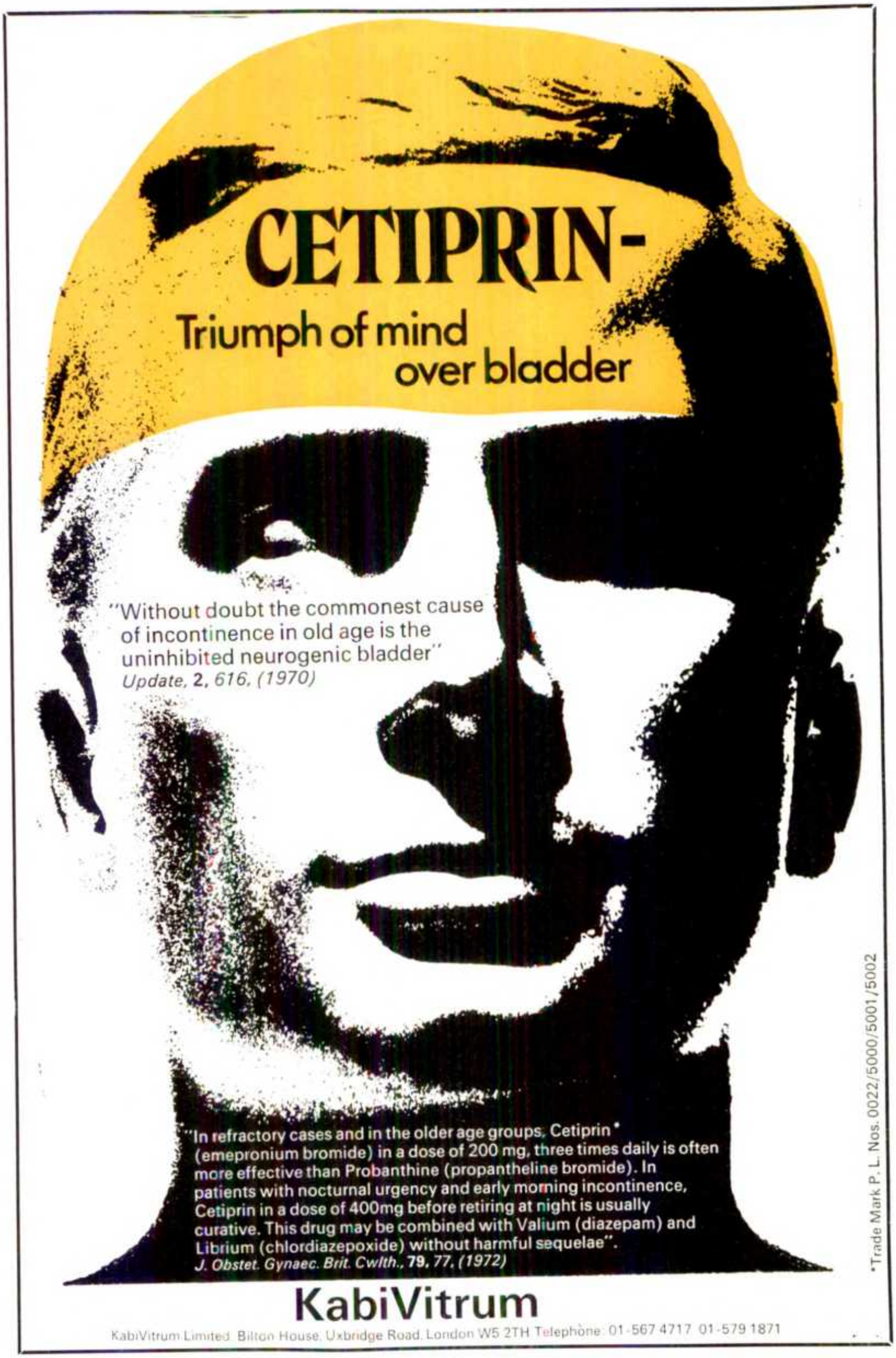

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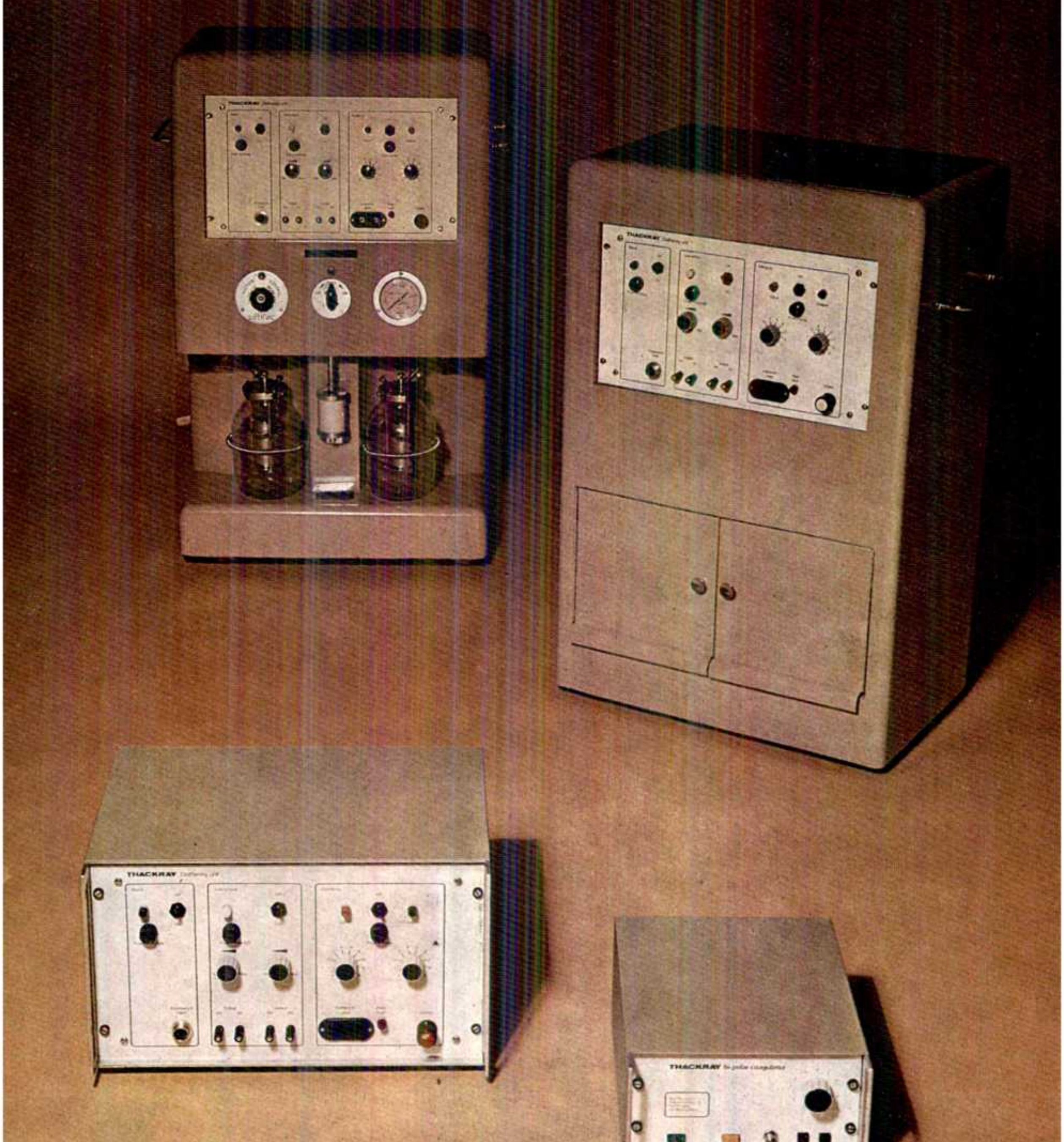

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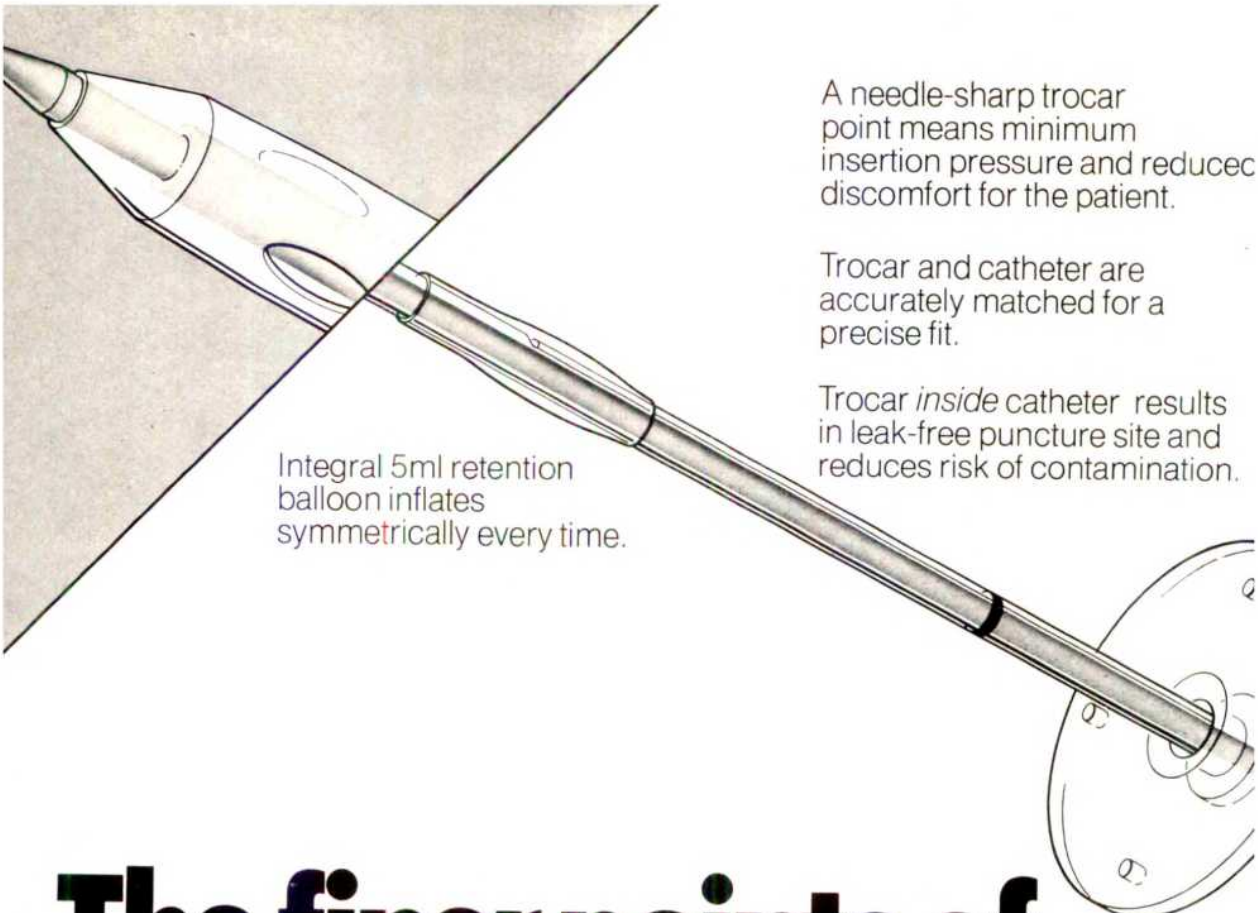

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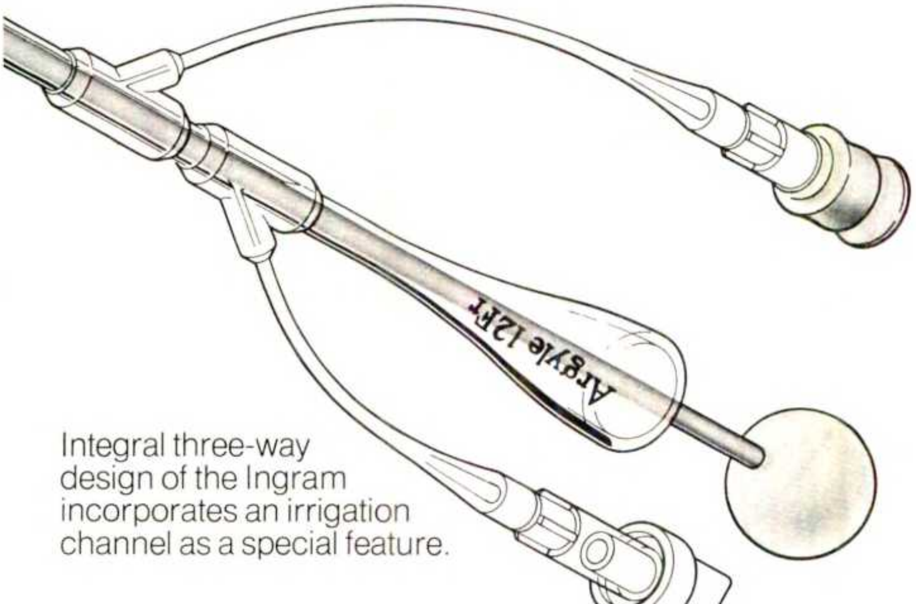

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The Relationship of the Urinary Cations, Calcium, Magnesium, Sodium and Potassium, in Patients with Renal Calculi

S. G. WELSHMAN and M. G. McGEOWN
Belfast City Hospital, Belfast

One of the main points of interest in the study of renal calculi formation has been the quantitative examination of urinary constituents. The high incidence of calcium-containing stones in hyperparathyroid and hypercalciuric patients seems closely related to an increased excretion of urinary calcium. However, it is also well established that a considerable number of people with high urinary excretion of calcium do not form stones, and that renal calculi often occur in patients who are normo-calciuric. In recent years, interest has been shown in the excretion of other urinary cations, particularly magnesium and sodium, which may increase the solubility of calcium crystals by displacing the calcium ions from the crystal lattice. Evans *et al.* (1967) found magnesium to be reduced in the 24-hour urines of stone-formers with a normal calcium excretion, and Oreopoulos, Soyannwo and McGeown (1968) reported significantly reduced magnesium/calcium ratios in the early-morning urines of fasting stone-forming patients. Modlin (1967) studied the excretion of sodium in stone-formers, whites and Bantu. He observed that white stone-formers exhibited both a reduced 24-hour sodium excretion and sodium/calcium ratio compared with normal white subjects, whereas the Bantu, who had a very low incidence of renal calculi, exhibited a very high sodium excretion. Controversy has arisen concerning the results of these investigations and also with regard to the use of ratios to compare the excretion of any two urinary constituents.

In this study, the mean 24-hour urinary excretions of calcium, magnesium, sodium and potassium was estimated in a large number of confirmed stone-formers in whom hyperparathyroidism could be fairly confidently excluded and the results compared with those of normal young adults and a large group of patients free of any renal disorders. The excretion of each constituent relative to calcium was determined by calculating the coefficient of correlation and the linear regression equation.

As stone-forming crystals may be deposited from highly concentrated urine samples, calcium, magnesium, sodium and potassium concentrations relative to creatinine were also determined in early-morning urine specimens of stone-formers and controls.

Only male subjects in the patient and control groups were used in this investigation as there is a marked sex difference in the excretion of calcium ions (Bulusu *et al.*, 1970; Davis, Morgan and Rivlin, 1970).

Material and Methods

24-hour urine collections were obtained from 101 male patients with calcium-stone disease admitted to the Belfast City Hospital over a 3-year period. The presence of this type of stone was confirmed by chemical analysis or by the presence of a dense radio-opaque stone in the renal tract. Patients with possible parathyroid disorders were excluded from this investigation, as were cases with renal tubular acidosis, sarcoidosis and vitamin D intoxication. As renal malfunction affects the urinary excretion of cations, all subjects with blood urea greater than 45 mg/100 ml were also excluded. 24-hour urine collections sent to the laboratory from 89 male patients with various non-renal diseases were used as patient controls. It was considered that results from a large number of patients might provide a more appropriate normal range for comparison with hospitalised stone-formers. A second set of normal controls was obtained from urine collections of 63 young male adults (aged 17 to 30 years), consisting of army personnel and laboratory workers. All subjects were on a free diet, except that stone-formers were encouraged to maintain a high fluid intake. It was assumed that individual variations in diet would be masked by the relatively large number of persons, from a homogeneous population, used in this investigation. The difference in diet at home and in hospital should be minimal, as every attempt is made by this hospital to provide a diet similar to that consumed by the patients at home.

Fresh early-morning specimens were obtained on wakening, from 43 normal male adults and from 41 male stone-formers. All subjects were selected by the same criteria used for the 24-hour collections.

Calcium was determined by an autoanalyser technique (Technicon Methodology N-3b), involving the reaction of cresolphthalein complexone and diethylamine with calcium. 8-hydroxyquinoline was added to the reaction to suppress interference by magnesium. Magnesium was estimated by the colorimetric reaction with Mann Yoe's azo dye, using a test kit produced by Roche Diagnostics. All calcium and magnesium results were rechecked by an atomic absorption spectrophotometric method. The tests were repeated if there was any significant difference in the results of the two methods. Sodium and potassium were analysed by flame emission spectrophotometry. Creatinine was determined by the alkaline picrate reaction, using an autoanalyser (Technicon Methodology N-11b).

Results

The mean 24-hour urinary excretions of calcium, magnesium, sodium and potassium were estimated for stone-formers, stone-free patients and young normal adults (Table I). There was no significant difference in the mean calcium, magnesium and sodium excretions between stone-formers and patient controls ($P > 0{\cdot}05$). Young adult controls showed no significant difference in calcium and magnesium excretion ($P > 0{\cdot}05$) when compared with stone-formers, but there is a highly significant increase in their sodium excretion ($P < 0{\cdot}001$). The mean urinary potassium excretion for stone-formers is significantly lower ($P < 0{\cdot}001$) than the values obtained from both control groups. When the results are expressed in relation to 1 g of urinary creatinine (Table II), the comparative excretion pattern of the 4 cations, between stone-formers and controls, remains unchanged, except that the stone-formers had a moderately significant increase in calcium compared with male patient controls ($P < 0{\cdot}05$).

A comparison of the 24-hour urinary excretions between calcium and magnesium, calcium and sodium, and calcium and potassium were determined by calculating the correlation coefficient and linear regression equations. The results for the 3 groups are shown in Table III. Significant correlations between the cation pairs for all groups were observed. Analysis of covariance was used to compare the linear regression lines of the stone-formers, patient controls and young adult controls, for each pair of cations. The regression lines for calcium on magnesium did not differ in either slope or position ($P > 0{\cdot}05$). There was also no significant difference in the 3 regression lines for calcium on sodium, for in either slope or position ($P > 0{\cdot}05$). The relative calcium and potassium excretions of stone-formers and patient controls were not significantly different ($P > 0{\cdot}05$) for slope and position. However, the regression line for the young adult controls had a significantly different slope ($P < 0{\cdot}001$) from the other 2 groups, indicating a greater increase of potassium excretion with increasing calcium excretion.

The creatinine concentrations of early-morning urine specimens from stone-formers and young adult controls were found to be approximately 100% greater than the values for the 24-hour collections (Table IV). The calcium, magnesium, sodium and potassium concentrations in the early-morning urines, expressed in terms of 1 g of creatinine, are given in Table V. The mean sodium and potassium concentration values for stone-formers and controls were not significantly different ($P > 0{\cdot}05$). The urines of stone-formers showed a significantly higher mean concentration

Table I

The mean 24-hour Urinary Excretions (±S.E.M.) of Calcium, Magnesium, Sodium and Potassium in Male Stone-formers, Patient Controls and Young Adult Controls

Group	No.	Calcium mg/24 hr	Magnesium mg/24 hr	Sodium mEq/24 hr	Potassium mEq/24 hr
Stone-formers	101	204 (8·7)	83 (3·5)	136 (5·8)	40 (1·3)
Patient controls	89	183 (8.9)	87 (3.7)	131 (5·8)	54 (2·0)
Young adult controls	63	213 (9.1)	90 (3.9)	174 (6·4)	65 (2·4)

Table II

The Mean Concentration per gram of Creatinine (±S.E.M.) of Calcium, Magnesium, Sodium and Potassium in 24-hour Urine Collection from Male Stone-formers, Patient Controls and Young Adult Controls

Group	No.	Calcium mg/l g Creat.	Magnesium mg/l g Creat.	Sodium mEq/l g Creat.	Potassium mEq/l g Creat.
Stone-formers	101	158 (6·9)	66 (2·4)	104 (4·9)	32 (1·3)
Patient controls	89	138 (6·7)	40 (2·9)	104 (5·2)	44 (1·8)
Young adult controls	59	146 (9·3)	64 (2·9)	127 (5·9)	47 (2·0)

Table III

The Linear Regression Equations and Correlation Coefficients for Calcium on Magnesium, Calcium on Sodium and Calcium on Potassium

	Linear Regression Equations	Correlation Coefficient	Probability t Test
Stone-formers	Magnesium = 44·2+0·19 calcium	r = 0·494	P<0·001
Patient controls	Magnesium = 62·8+0·13 calcium	r = 0·442	P<0·001
Young adult controls	Magnesium = 51·4+0·18 calcium	r = 0·556	P<0·001
Stone-formers	Sodium = 83·1+0·26 calcium	r = 0·341	P<0·001
Patient controls	Sodium = 94·4+0·21 calcium	r = 0·305	P<0·01
Young adult controls	Sodium = 120·6+0·29 calcium	r = 0·471	P<0·001
Stone-formers	Potassium = 32·1+0·04 calcium	r = 0·301	P<0·01
Patient controls	Potassium = 47·0+0·04 calcium	r = 0·231	P<0·05
Young adult controls	Potassium = 39·2+0·12 calcium	r = 0·477	P<0·001

Table IV

Creatinine Concentrations in mg% for 24-hour Urine Collections and Early-morning Urine Specimens from Stone-formers and Controls

	24-hour Urine		Early-morning Urine	
Group	No.	Mean Creatinine mg%	No.	Mean Creatinine mg%
Stone-formers	97	63	42	125
Young adult controls	63	97	43	198

Table V

Mean Calcium, Magnesium, Sodium and Potassium Concentrations per gram Creatinine in Early-morning Urines of Stone-formers and Controls. Standard Error of Mean in Brackets

Group	No.	Calcium mg/l g Creat.	Magnesium mg/l g Creat.	Sodium mEq/l g Creat.	Potassium mEq/l g Creat.
Stone-formers	41	111 (10·9)	56 (4·0)	69 (5·9)	25 (1·9)
Young adult controls	43	80 (7·0)	74 (5·2)	74 (7·2)	26 (2·4)

of calcium ($P < 0 \cdot 05$), and a significantly reduced magnesium ($P < 0 \cdot 01$), compared with those of the controls. There was no significant difference ($P > 0 \cdot 05$) in slope or position between the calcium on magnesium regression lines of stone-formers ($Mg = 27 \cdot 2 \pm 0 \cdot 26\, Ca$) and controls ($Mg = 49 \cdot 0 \pm 0 \cdot 31\, Ca$).

Discussion

Normal values for calcium, magnesium, sodium and potassium were obtained by analysing the 24-hour urine collections from young healthy males. As this group may not give a true normal comparison with hospitalised stone-formers, for reasons of differences in age, activity and physical fitness, a second set of controls was acquired from the urines of a large number of hospital in-patients known to be free of any renal abnormalities.

The mean daily excretion of urinary calcium for the normal controls was similar to the values obtained by Sutton and Watson (1969) and Bulusu *et al.* (1970). The stone-formers, however, did not differ significantly in the daily calcium excretion from these normal controls. This is contrary to the observations of Evans *et al.* (1967), Bulusu *et al.* (1970) and White *et al.* (1969), who found the mean daily calcium excretion for male idiopathic stone-formers to be 380 mg, 338 mg and 320 mg respectively. However, King *et al.* (1968) obtained values of only 211 mg per 24 hours and a mean value of 200 mg for young adult male controls. According to King (1971) only about 10% of stone-formers excreted more than 300 mg of calcium per day. In the present series the percentage of hypercalciurias (urinary calcium > 300 mg per 24 hours) in male stone-former, patient control and young adult control groups were 11·8, 10·2 and 10·8 respectively.

The normal 24-hour magnesium excretions were similar to those given by Sutton and Watson (1969), while Evans *et al.* (1967) and Modlin (1967) obtained higher values for urinary magnesium in normal controls. According to the latter, there was no difference in the magnesium excretion between stone-formers and normal controls, but they found that stone-formers with normal calcium excretion showed a significant reduction in urinary magnesium. The results in this investigation suggest that no significant difference in magnesium excretion exists between any of the groups, in spite of the fact that most of the stone-formers are normocalciuric. With regard to the concentrations of calcium and magnesium, relative to creatinine, in early-morning urine, a moderately significant increase in calcium, and reduction in magnesium were observed for stone-formers compared with controls. These findings may be of some significance, as it is probable that the concentrated urine specimens are responsible for the deposition of stone-forming material.

It has been reported by King *et al.* (1968) that the majority of stone-formers have an abnormally high calcium/magnesium ratio, calculated from 24-hour excretion values. When Oreopoulous *et al.* (1968) estimated the calcium/magnesium ratios from the calcium and magnesium concentrations in early-morning urine of stone-formers and controls, a significant increase in the mean calcium/magnesium ratio was observed in the stone-former's urine. The validity of ratios to relate 2 constituents and to compare these ratios between different groups have been criticised by Papadimitriou and Ram (1968) and Sutton and Watson (1968). In this study, the correlation coefficient and linear regression equation for 24-hour calcium on magnesium in each group were determined. The correlation was found to be highly significant in all groups, but there was no significant difference in the linear regression lines for calcium on magnesium between stone-formers and controls. With regard to the examination of early-morning urines, there was no significant difference in the calcium on magnesium linear regression equations for stone-formers and controls, in spite of the differences in calcium and magnesium concentrations. These results confirm the view that the use of ratios to compare excretory patterns between groups may be misleading.

Modlin (1967) estimated sodium and calcium in white controls, Bantu and stone-formers. The Bantu, who are relatively free of stone disease, were reported to have a significantly higher excretion of sodium than normal white subjects, while stone-formers had a much lower excretion of sodium than normal controls. It was also stated that the mean sodium/calcium ratio was significantly lower in stone-formers than in white controls, and that the sodium/calcium ratio for the Bantu was much higher than the other two groups. On this evidence it was postulated that a high level of urinary sodium, and particularly an elevated sodium/calcium ratio, may prevent the occurrence of renal calculi. However, it has been found in this survey that stone-formers and normal controls excreted similar amounts of sodium per day. The young adult controls are exceptional in the fact that they excrete a greater amount of sodium, paralleling their increased excretion of other cations. The disparity between results for male patient controls (average age 47 years) and young healthy adults (average age 22 years) may be the reason for differences in interpretation of other workers. The relationships of calcium to sodium, expressed by the linear regression equations, were not significantly different.

The urinary potassium excretion of male stone-formers was unexpectedly low in comparison with the values for both normal patients and young adults. There was no significant difference in the linear regression equations of stone-formers and patient controls, although it appears that the former have a lower excretion of potassium relative to calcium. There was no evidence to suggest that the potassium levels in the diet of stone-formers differs from that of the normal population. At present, no obvious explanation can be found for the low 24-hour potassium excretion of stone-formers.

The early-morning urines of stone-formers and young adult controls have similar concentrations of sodium and potassium relative to creatinine.

Conclusion

The 24-hour urinary excretions of calcium, magnesium and sodium by male idiopathic stone-formers do not appear to be significantly different from normal male controls. Potassium excretion by stone-formers, however, was significantly lower than the controls. A moderately significant increase in calcium and a reduction in magnesium, relative to 1 g of creatinine, were observed in early-morning urines of patients with renal calculi. These abnormalities in concentrated urine samples which pass slowly through the renal tract overnight may be an important factor in the initiation and development of calcium-containing stones.

Summary

Calcium, magnesium, sodium and potassium were estimated in the 24-hour urine collections of 101 idiopathic male stone-formers, 89 male patient controls and 59 young male adult controls.

The results were calculated in terms of 24-hour volume and 1 g of creatinine. The concentrations of the 4 cations, relative to a gram of creatinine, were also determined in the early-morning urines of 41 male stone-formers and 43 young male adult controls.

No difference was observed in the 24-hour excretion of calcium, magnesium and sodium between the stone-formers and controls. The mean daily potassium excretion, however, was significantly reduced in the urine of stone-formers.

The linear regression equations were calculated for calcium on magnesium, calcium on sodium, and calcium on potassium, using the 24-hour excretion values of these cations. Only the calcium on potassium line of stone-formers was significantly different from that of the normal subjects.

A significant increase by stone-formers in the urinary calcium concentration of their early-morning specimens was found. The high concentration of urinary calcium in overnight urines of stone-formers combined with a low magnesium concentration might possibly contribute to the development of renal stone disease.

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Evaluation of Differential Renal Function Studies in Segmental Renal Artery Occlusion

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Experience regarding diagnosis and treatment of renovascular hypertension has accumulated in the last 20 years. Differential renal function studies have significantly contributed to the diagnosis of such cases and have helped to establish which of these cases will benefit from surgery. Yet, in spite of this experience, the number of well-documented cases with segmental renal ischaemia, in whom differential renal function studies were performed, is small (Stamey *et al.*, 1961; Stamey, 1963; Howard and Connor, 1964; Hunt *et al.*, 1966; Kropp and O'Conor Jr, 1968; O'Conor Jr and Simon, 1970; Fair, 1970; Fournier *et al.*, 1973).

In 1961 Stamey described an accurate, sensitive and reproducible method of differential renal function studies to detect patients with curable hypertension due to functionally significant occlusions of the main renal artery. The same method permitted for the first time the diagnosis of functionally significant segmental renal artery stenosis. The details of the method and the prognostic value of these studies have been well recorded (Stamey, 1963; Stamey, 1966; Palmer, 1971).

It is the purpose of this paper to present additional cases with suspected segmental renal ischaemia, to clarify the difficulties which sometimes arise in the presence of positive function studies compatible with functionally significant segmental renal artery stenosis and to comment on some haemodynamic aspects, as expressed by such studies.

Methods and Patients

All of the patients were on a normal salt diet for at least 2 weeks prior to the study; during the same period no antihypertensive therapy, diuretics or sedatives were administered. The differential renal function studies were performed according to the technique established by Stamey (1961, 1963). There were no complications in these studies.

Cure was defined as an ambulatory blood pressure of 150/90 mm Hg or less, 1 year following the operation without medication.

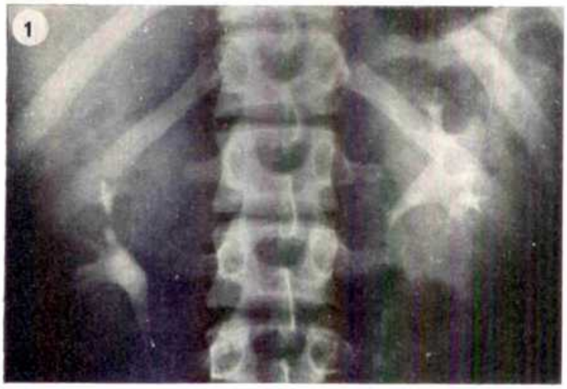
Case 1. H. F., a 20-year-old male non-identical twin, was admitted on 3rd March, 1969, because of hypertension.

At the age of 16 a routine physical examination had revealed a blood pressure of 170/100 mm Hg. For the next 4 years blood pressure levels lay between 170/90 and 170/105 mm Hg. Past history and family history were negative for renal or cardiovascular disease.

Physical examination on admission showed a young man in good general condition with a blood pressure of 170/110 mm Hg. The ECG showed left ventricular hypertrophy with slight ischaemic changes.

Rapid sequence and washout intravenous pyelograms showed normal-sized kidneys with smooth outlines. Contrast excretion appeared simultaneously in both kidneys. After hydration the contrast medium showed greater intensity in the right kidney (Fig. 1). A right percutaneous transfemoral arteriogram (Fig. 2) demonstrated normal main renal arteries for both kidneys. A bilateral selective renal arteriogram revealed two stretched apical arteries to the upper pole with scanty abnormal arborisation, one arising from the distal part of the right main renal artery and another one from the upper part of its anterior branch (Fig. 3). The left renal artery and its branches were normal.

Ureteric catheterisation studies (Table I) showed a pattern compatible with functionally significant right segmental artery stenosis. There was a more than 1 : 2 difference in urine flow rate between the two kidneys (R < L)



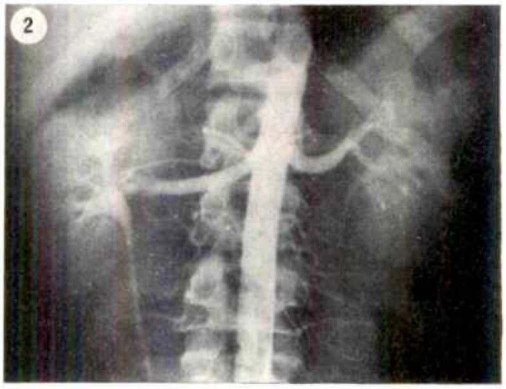


Fig. 1. Case 1. 26-minute washout pyelogram shows increased density of contrast material in the right renal collecting system.
Fig. 2. Case 1. Transfemoral renal arteriogram shows normal main renal arteries bilaterally.

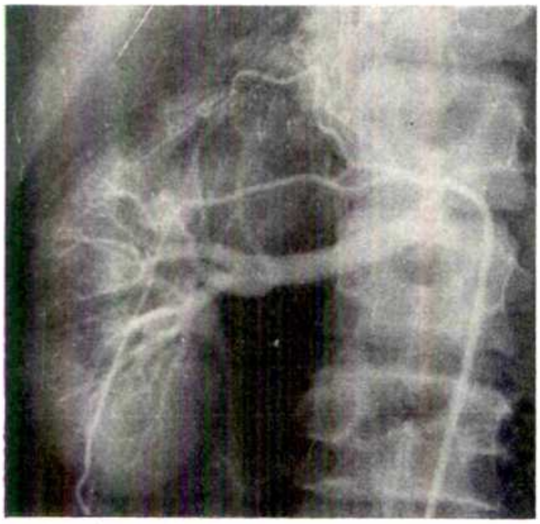


Fig. 3. Case 1. Selective right renal arteriogram demonstrates two stretched arteries with poor arborisation in the upper renal pole. The rest of the renal vascular tree appears normal.

and a greater than 16% increase in the PAH urine concentration of the right kidney as compared to that of the left side. Urine sodium concentration was decreased by 22% on the affected side. The renal plasma flow (RPF) of the right kidney, as measured by C_{PAH}, was 373 ml/min, whereas it was 381 ml/min on the left side.

With the evidence of functionally significant segmental renal artery occlusion in the right upper kidney pole, and in the presence of a high contralateral renal plasma flow (>250 ml/min), the patient was explored through a right flank incision. Meticulous dissection of the renal artery and its branches as far as their entry to the parenchyma did not reveal any definite areas of stenosis. Since no area of ischaemia was visible, and being certain that curable segmental ischaemia was present in the right kidney from the split renal function data (after having ruled out main renal artery stenosis), the right kidney was removed.

On low-pressure hypaque injection of the main renal artery of the removed kidney (Fig. 4, A), the apical artery arising from the main renal artery was not seen. After injection of the dye with increased pressure (Fig. 4, B), this apical artery was visualised and a 4 mm defect was revealed at its origin. The remainder of this artery was thin and stretched. The apex of the kidney contained less dye than the rest of the parenchyma.

The kidney weighed 120 g and its surface was smooth. The main renal artery and its branches were all normal but for a segmental stenosis of one apical branch. This was due to marked muscular hyperplasia alternating with areas where the muscle was of normal thickness. The intima was normal throughout (Fig. 5). The picture was typical for sausage-like constrictions and was compatible with right apical artery stenosis due to fibromuscular dysplasia

Table I

Differential Renal Function Studies in Functionally Significant Right Segmental Renal Artery Occlusion (Case 1)*

		I	C	I/C
V	(ml/min)	2·3	5·1	0·45
U_{In}	(mg/100 ml)	641	318	2·02
U_{PAH}	(mg/100 ml)	313	145	2·16
U_{Na}	(μEq/ml)	62	91	0·68
C_{In}	(ml/min)	58·95	64·99	0·91
C_{PAH}	(ml/min)	373·44	380·54	0·98
FF	(C_{In}/C_{PAH})	0·18	0·21	0·86

* Each value signifies average figure for 3 consecutive 10-minute collection periods. V signifies urine flow rate; U_{In}—inulin urine concentration; U_{PAH}—PAH urine concentration; U_{Na}—sodium urine concentration; C_{In}—inulin clearance; C_{PAH}—PAH clearance; FF—filtration fraction; I—ischaemic kidney; C—contralateral kidney; I/C—ratio of ischaemic value divided by contralateral.

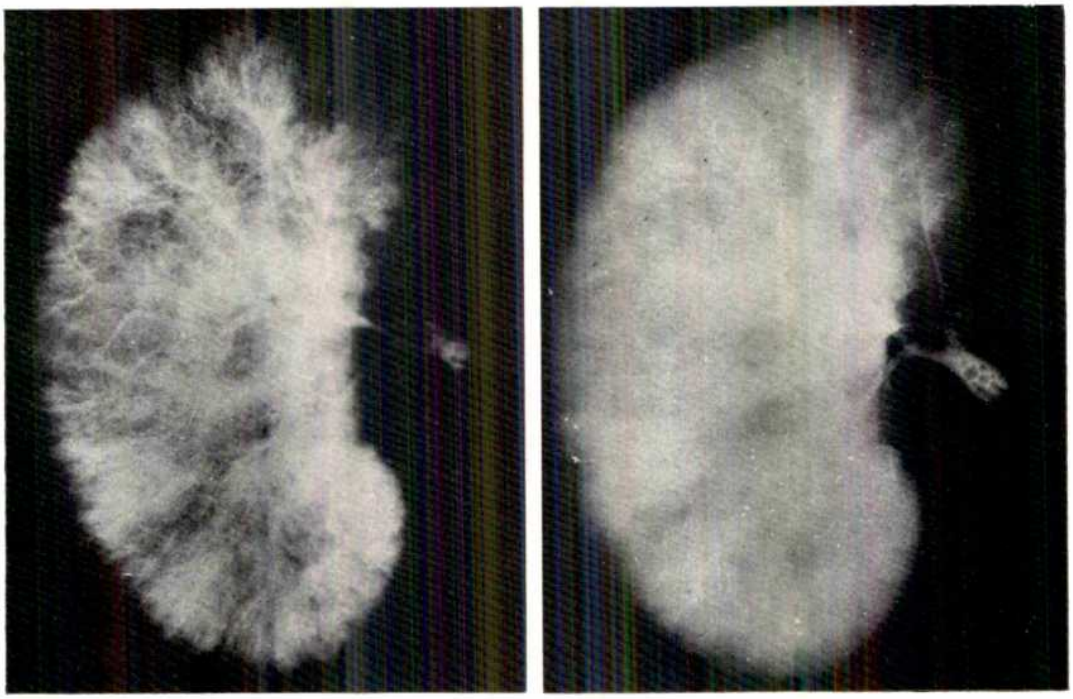

A B

Fig. 4. Case 1. A, Low-pressure hypaque injection of removed right kidney reveals absence of opacification of the apical artery arising from the main renal artery. Note the defect in the uppermost part of the kidney. B, High-pressure hypaque injection of removed right kidney reveals the apical artery arising from the main renal artery with a 4 mm long defect near its origin. Note again the defect in the uppermost part of the kidney.

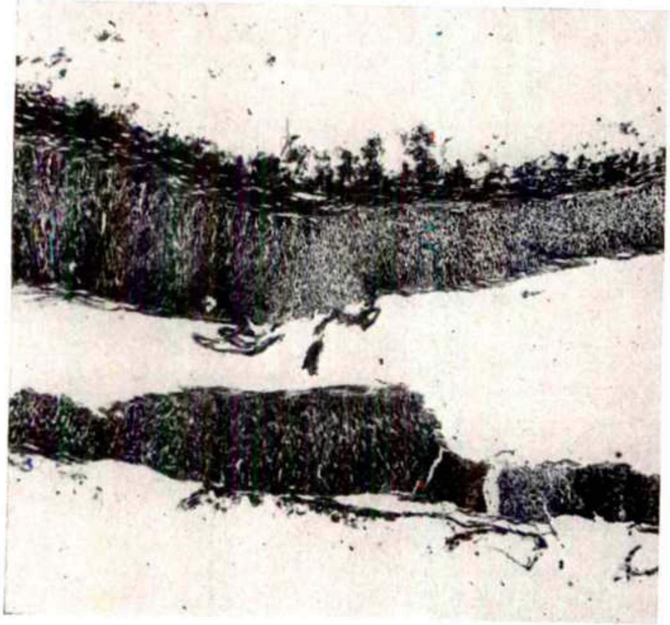


Fig. 5. Case 1. Microscopic longitudinal section of the apical branch of the right main renal artery. Note the irregular thickness of the media with an area of marked narrowing of the lumen. Masson's trichrome. ×42.

(medial fibroplasia). However, no signs of ischaemic tubular atrophy were detected. In the upper kidney segment prominent juxtaglomerular bodies (JGB) were counted in more than 60% of the glomeruli and an average of 15 cells was found in each of them (Fig. 6), while in the lower segment the JGB's were normal.

During the days following nephrectomy, the patient's blood pressure fell gradually to 130/60-140/80 mm Hg and remained so. Three years later blood pressure levels ranged between 130/75 and 145/90 mm Hg.

Case 2. G. D., a 37-year-old mother of 7 healthy children, was admitted on 8th June 1970, because of hypertension. A blood pressure of 120/80 mm Hg was measured during her last pregnancy in 1966. Repeated levels of between 220/120 and 250/140 mm Hg were observed just before the present admission. Past history and family history were negative for renal or cardiovascular disease.

Physical examination on admission showed a fat woman in good general condition with a blood pressure of 210/140 mm Hg. Funduscopic examination revealed vasospasm and some exudates were observed. A systolic murmur was heard over the cardiac area.

ECG showed some ischaemic changes. Chest X-ray revealed marked hypertrophy of the heart; the left ventricle was enlarged, the aorta dilated. The intravenous pyelogram (IVP) was normal except for some irregularities in the lower half of the lateral border of the left kidney, compatible with scars. A left brachial aortogram (Fig. 7) demonstrated an elongated aorta with an irregular marginal outline, indicative of atherosclerosis. The main renal arteries were normal. There was a small (2 mm wide) lower polar artery to the left kidney, originating about 2 cm below the left main renal artery and presenting a stenosis at its distal part. Beyond the stenosis the polar artery split into small irregular branches showing poor contrast density as compared with similar size arteries originating from the main renal artery. The area supplied by the left lower polar artery showed poor blood supply.

Differential renal function studies (Table II), showed a difference of only 18% in urine flow rate between the 2 kidneys, and a 21% increase in the urine PAH concentration of the left kidney, as compared to the right side. The glomerular filtration rate (GFR) was 10% less in the left kidney than in the right, but renal plasma flow (RPF) was identical in both kidneys (254 ml/min).

This functional pattern can be seen in "essential" hypertension but is not compatible with functionally significant segmental renal artery stenosis. Thus, the lower polar artery stenosis could not have caused the high blood pressure in this patient. However, in spite of the negative split renal function studies, it was felt that left lower partial nephrectomy should be proposed to the patient as the only chance to cure her high blood pressure because of her relatively young age, negative family history of hypertension, and the limited surgical procedure involved.

On exploration the whole kidney presented a normal vascular colour. The whole lower pole was resected. A needle biopsy of the upper pole of the kidney was also performed.

Histological sections of the segmental artery showed concentric fibrous intimal thickening (Fig. 8). The resected

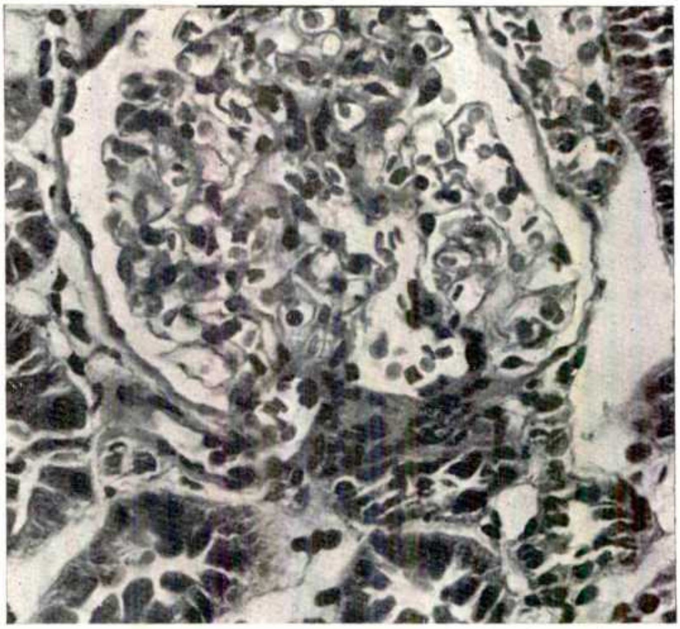


Fig. 6. Case 1. Microscopic section of right upper pole. The juxtaglomerular body is prominent and there is an increase in the number of juxtaglomerular apparatus cells. H & E. ×420.

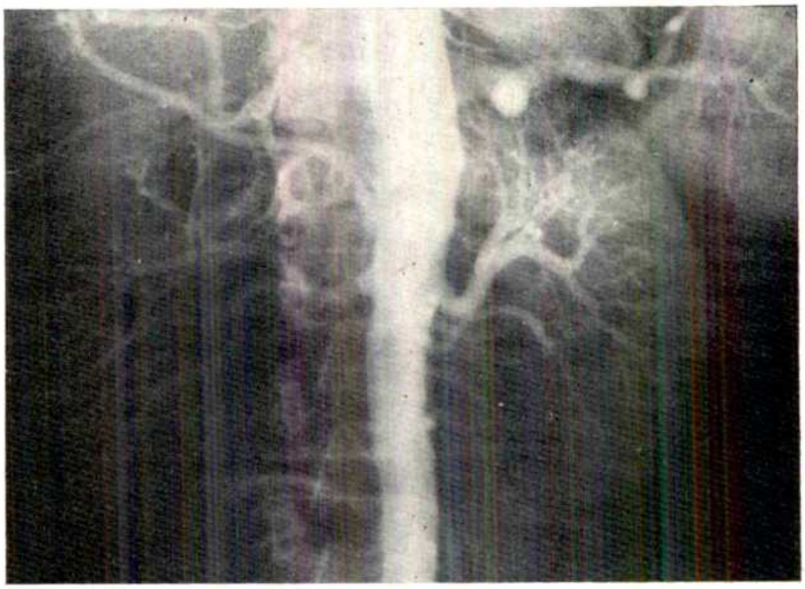


Fig. 7. Case 2. Left ulnar artery aortogram shows normal right renal artery; in addition to a normal left main renal artery, a small lower polar artery is seen on the left side. The distal part of this lower polar artery is slightly irregular and shows an abrupt end before splitting into irregular small branches. Note irregular outline of the lower pole.

Table II

Differential Renal Function Studies in Essential Hypertension with Functionally Insignificant Left Segmental Renal Artery Stenosis (Case 2)*

		I	C	I/C
V	(ml/min)	9·5	11·6	0·82
U_{In}	(mg/100 ml)	148	134	1·10
U_{PAH}	(mg/100 ml)	52·3	43·1	1·21
U_{Na}	(μEq/ml)	89	93	0·96
C_{In}	(ml/min)	58·52	64·70	0·90
C_{PAH}	(ml/min)	253·85	254·06	1·00
FF	(C_{In}/C_{PAH})	0·23	0·25	0·92

* Legend as for Table I.

Table III

Differential Renal Function Studies in Essential Hypertension (Case 3)*

		I	C	I/C
V	(ml/min)	5·30	10·10	0·52
U_{In}	(mg/100 ml)	243·00	161·00	1·51
U_{PAH}	(mg/100 ml)	107·00	60·60	1·77
U_{Na}	(μEq/ml)	63·00	89·20	0·71
C_{In}	(ml/min)	57·13	71·46	0·80
C_{PAH}	(ml/min)	321·66	342·97	0·94
FF	(C_{In}/C_{PAH})	0·18	0·21	0·86

* Legend as for Table I.

lower pole revealed foetal lobulations, but was otherwise normal. However, a few small cortical scars and moderate arterio- and arteriolosclerosis were noted. Similar changes were observed in the biopsy of the upper pole.

Following operation, there was no change in the blood pressure, which fluctuated between 180/110 and 230/150 mm Hg. The patient was therefore placed on antihypertensive therapy. One year later a blood pressure of 178/125 mm Hg was measured.

These 2 cases show the value of differential renal function studies in accurately predicting the outcome of surgery in hypertensive patients with documented segmental renal artery stenosis.

A positive split renal function study for functionally significant segmental renal artery occlusion, however, is not sufficient alone to assure cure of hypertension and should always be confirmed by a corresponding arteriographic finding.

This fact was emphasised recently (Fair and Stamey, 1971), but Stamey had already pointed out in 1963 that a 1 : 2 difference in urine flow rate between the 2 kidneys (ischaemic/non-ischaemic) accompanied by a 16% or greater increase in PAH urine concentration from the ischaemic kidney can represent, in the hypertensive patient, not only curable segmental renal ischaemia with a contralateral normal kidney but also "essential hypertension" with bilateral small vessel disease due to arteriosclerosis, disparate glomerulonephritis, or bilateral fibromuscular hyperplasia of the renal arteries.

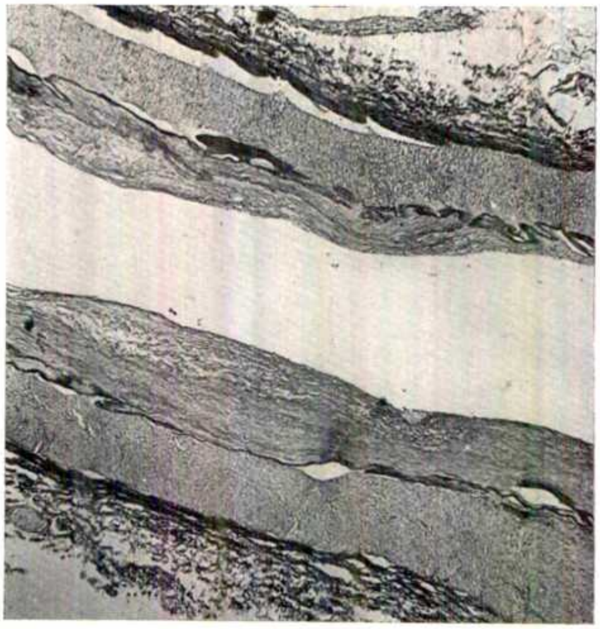


Fig. 8. Case 2. Microscopic longitudinal section of the left lower polar artery showing marked fibrous intimal thickening. Verhoeff—Van Gieson. ×42.

This observation is well demonstrated by the following hypertensive patient who presented a pattern of split renal function studies compatible with curable segmental ischaemia but in whom segmental renal artery stenosis was not demonstrated on angiography.

Case 3. L. E., a 36-year-old man, had a 15-year history of high blood pressure (160-220/110-140 mm Hg). The only positive finding in the pyelogram was the different size of the kidneys (the right kidney measured 12·5 cm, the left kidney 15·5 cm). The aortogram showed normal main and segmental renal arteries bilaterally. The nephrogram appeared somewhat later on the right side. The lower pole of the right kidney was atrophied to a certain degree. Differential kidney function studies of this patient (Table III) revealed a typical pattern for curable segmental ischaemia in the right kidney. On the basis of differential renal function studies and a possible atrophy of the right renal lower pole, the right kidney was removed. It weighed 190 g, and on histological examination marked arterio- and arteriolosclerosis was evident. No narrowing of the lumen of the main renal artery and its branches was demonstrated. The blood pressure remained unchanged after the nephrectomy and the patient has been under continuous antihypertensive therapy since then. In this case the lack of response to surgery cannot be attributed to a reduced blood flow to the contralateral kidney as its C_{PAH} was 343 ml/min.

Discussion

The divided renal function studies, as defined by Stamey (1961), demonstrated for the first time that the functional lesion characteristic of renal ischaemia is *qualitatively* the same in main and segmental renal artery stenosis, but *quantitatively* different. Thus, the criteria for functionally significant main renal artery stenosis are a 1 : 3 differential in urine flow rate between the 2 kidneys (ischaemic/contralateral) with at least a 100% increase in the p-aminohippurate (PAH) urine concentration from the affected kidney, whereas for functionally significant segmental renal artery occlusion a difference of only 1 : 2 in urine flow rate with at least 16% increase in PAH urine concentration from the ischaemic kidney is enough. Furthermore, these divided renal function studies are not only diagnostic but also prognostic. In other words, the cure of a patient's hypertension depends not only upon the presence of a positive study for unilateral functionally significant renal artery occlusion but also upon the degree of reduced blood flow due to diffuse small vessel disease in the contralateral kidney as measured by its RPF. Surgery will usually benefit patients if the RPF of the non-ischaemic kidney is 250 ml/min or greater (Stamey, 1966; Palmer, 1971).

An extremely interesting observation in the first patient (F. H.), in whom divided renal function studies demonstrated curable segmental ischaemia and surgery cured the hypertension, was that in spite of a minimal difference in renal plasma flow (C_{PAH})—only 2%—between the two kidneys, there were highly significant differences in urine flow rate and in PAH, inulin and sodium urine concentrations. Hypaque injection of the removed ischaemic kidney confirmed this physiological finding, showing involvement of only the apical area. There was virtually no difference in renal mass between the two kidneys in this patient. This is the smallest reduction in RPF ever observed in an ischaemic kidney due to functionally significant segmental renal artery occlusion according to our knowledge, and demonstrates that even very small reductions in renal plasma flow are able to produce excessive water and sodium reabsorption and subsequent stimulation of renin secretion. In fact, it has already been mentioned that the greatest increase in reabsorption of water and sodium in the ischaemic kidney occurs in those kidneys with the smallest reduction in RPF and GFR (Stamey, 1963; 1966). This case shows once more the sensitivity of differential function studies based on urea osmotic diuresis in the detection of curable segmental ischaemia, and demonstrates that the differences in RPF and GFR between the 2 kidneys account for only a negligible part of the difference in urine flow rates, whereas excessive water reabsorption is responsible for virtually the total difference in urine flow; it also suggests that screening methods for detection of renovascular hypertension, based only on comparative measure of renal plasma flow (C_{PAH}) and not of urine flow rates, cannot be reliable and may exclude potentially curable patients from further study and adequate treatment. This case also raises the question of the validity of the theoretical deductions of the authors (Fair and Stamey, 1971) who try to prove that small ischaemic areas may produce differences in urine flow rate and PAH urine concentration between the 2 kidneys less than required by the original criteria in a positive function study for curable segmental ischaemia.

Despite the explanations, the discrepancy between the differences in RPF(C_{PAH}) and urine flow rate in our patient remains very striking and raises a question. Could it not be possible that some degree of additional ischaemia occurs also in the nephrons adjacent to the ischaemic area, due to the segmental renal artery stenosis, and as a result secretion of urine in the adjacent nephrons is reduced and its quality is the same as that secreted in the ischaemic apical area?

Another interesting observation, mentioned also by other investigators (Stamey, 1966; Fair, 1970), is the reduced filtration fraction (FF) of the ischaemic kidney as compared to that of the contralateral kidney (Table I) in this patient. This was due to the fact that the GFR was 9% less and the RPF only 2% less in the ischaemic kidney than in the contralateral kidney. The reduced filtration fraction in the ischaemic kidney as a result of the bigger reduction in its GFR may explain why the diagnostic differences between the two kidneys in U_{PAH} (2·16 in our patient) are greater than those in U_{In} (2·02). PAH is secreted into an initial smaller glomerular filtrate in the ischaemic kidney (GFR : 59 ml/min) than in the non-ischaemic one (GFR : 65 ml/min). Thus, before water reabsorption starts, the PAH concentration in the proximal tubule of the ischaemic kidney is already greater than that in the contralateral kidney. The concentration of inulin, which is handled only by filtration, will be the same in the proximal tubules of both kidneys. Since neither inulin nor PAH are reabsorbed in the tubule, the final urine from the ischaemic kidney will have a higher concentration of PAH than inulin.

The higher PAH urine concentration in the ischaemic kidney could also be explained in another way. It was demonstrated experimentally by Vogel and Kröger (1965) that PAH transport in the proximal tubule is linked to sodium transport, but, interestingly enough, the transport of these 2 substances occurs in opposite directions. In other words, the more sodium that is reabsorbed, the more PAH is secreted into the tubule. Since more sodium is reabsorbed in the tubules of the ischaemic kidney than the contralateral one, more PAH will be secreted and, as a result, the final

PAH urine concentration of the ischaemic kidney will be higher than the inulin urine concentration.

We could not confirm McDonald's (1968) experience in which 15 out of 16 hypertensive patients with functionally ischaemic unilateral "small" kidneys but without renal artery stenosis, were cured of the hypertension after nephrectomy. McDonald established his own criteria of functional ischaemia for this kind of lesion: at least a 1 : 2 difference in urine flow rate between the 2 kidneys and a 70% or greater increase in PAH urine concentration from the ischaemic kidney (which, by the way, is compatible with Stamey's pattern for functionally significant segmental renal artery occlusion). Our patient, L. E., who had a smaller right kidney, no main renal artery stenosis and fulfilled McDonald's criteria for functional ischaemia, did not benefit from the nephrectomy as was already mentioned. But then, the author did not specify how small a kidney has to be for such a hypertensive patient to benefit from surgery.

In a recent paper (Fair and Stamey, 1971) the authors contend that in their experience a significant number of hypertensive patients with functionally significant segmental renal ischaemia, cured by surgery, did not show the expected patterns in the split renal function studies as defined originally by Stamey (1961). Therefore, they concluded that adherence to the previous criteria may be misleading. In fact, 2 out of their 11 reported cases were not examined under urea osmotic diuresis, as required in this kind of split renal function studies. 8 of the 9 remaining cases presented patterns conforming to Stamey's original criteria. That these original criteria are as valuable today as before was also confirmed in similar cases by us (our first case) and other authors (Kropp and O'Conor Jr, 1968; O'Conor Jr and Simon, 1970).

In another case (Geyskes *et al.*, 1972) the authors observed in the split renal function studies of a patient with functionally significant segmental renal artery occlusion the absence of increased PAH urine concentration from the affected kidney despite some difference in urine flow between the two kidneys. This could have occurred as a result of the differential renal function studies having been done under water and not urea osmotic diuresis (Shapiro, 1973). Had this patient been studied under urea osmotic diuresis, it is quite possible that the study would have shown the characteristic pattern from curable segmental ischaemia: a 50% ratio in urine flow rate between the two kidneys and a 16% or greater increase in urine PAH concentration from the ischaemic kidney.

In our first case segmental renal artery stenosis was due to medial fibroplasia and morphological evidence for increased renin secretion was found in the form of marked juxtaglomerular apparatus hyperplasia. This was in fact the only histological abnormality in an otherwise normal appearing renal cortex. In Stamey's experience (1963), all such patients were cured of their hypertension, as was also our patient.

On the other hand, in our second case the histological features of the renal lesion were those of nephrosclerosis, although segmental renal artery stenosis was found by X-ray and morphological examination.

In the last case, segmental renal artery occlusion could not be demonstrated by the pathologist, although split renal function studies suggested curable segmental ischaemia. The histological features were those of nephrosclerosis.

Conclusion

Differential renal function studies, based on urea osmotic diuresis, cannot alone assure the diagnosis of curable renovascular hypertension due to functionally significant segmental renal ischaemia. Even when positive, according to the criteria established by Stamey, these studies have always to be confirmed by a compatible arteriographic finding.

In the presence of a well-visualised segmental renal artery stenosis on angiography, differential renal function studies are of importance in correctly evaluating which hypertensive patients will be cured by appropriate surgery. Furthermore, carefully performed studies are informative about physiological changes occurring in the ischaemic kidney and the degree of blood flow to the contralateral kidney.

It is suggested that cure of renovascular hypertension can be reasonably expected only in the patient in whom both tests (renal angiography and differential renal function studies) are positive for curable segmental ischaemia.

Summary

3 patients with suspected renal segmental ischaemia are presented. In 2 of them segmental renal artery stenosis was demonstrated radiographically and the differential renal function studies predicted the outcome of surgery accurately. In the last patient no segmental renal artery stenosis was demonstrated on angiography, and surgery did not benefit this patient in spite of positive differential renal function studies for "curable" renal segmental ischaemia.

Some haemodynamic aspects, as expressed by the differential renal function studies, are discussed.

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The Radiological Diagnosis of "Avascular" Renal Tumours

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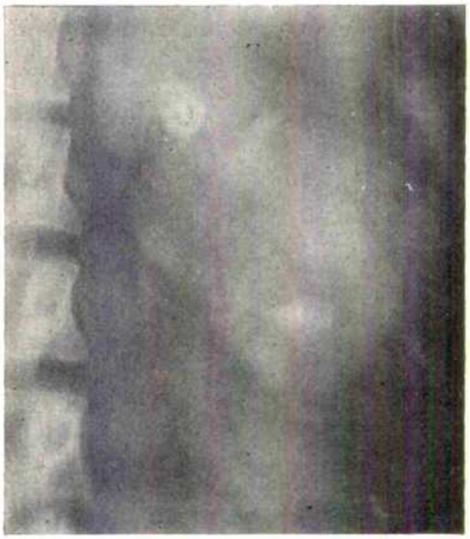
It is commonly believed that angiograms alone may distinguish between benign and malignant renal masses by the absence or the demonstration of a "tumour" circulation. The commonest renal space-occupying lesions are cysts. Moderate or large sized cysts, *e.g.* 5 to 10 cm in diameter, occur about 10 times as frequently as renal tumours, whilst small cysts are extremely common. Since cysts do not have any concomitant abnormal circulation (unless a renal tumour is present adjacent to a cyst), the absence of an abnormal circulation is often held to be good evidence that the lesion is a cyst. Such a thesis is also the basis of the radioactive "blood-pool" scan with the demonstration of vascular or avascular areas in the kidney. When positive such a scan is obviously useful, but when negative the result should be interpreted with caution. The same is true about angiograms which fail to demonstrate a tumour type of circulation.

Evans (1957) pointed out that about 10% to 20% of renal tumours were avascular by his intravenous angiographic method of examination using large doses of contrast medium delivered through angiocardiography syringes and cannulae in veins in both arms. The single radiograph taken in the angiographic phase was followed by tomograms ("nephrotomography"). Woodruff and Ottoman (1956) claimed that less than one-third of all renal tumours would not show abnormal vessels. Edsman (1957) found abnormal vessels in 75 out of 80 cases. In 3 of the 5 avascular masses the irregular edge of the neoplasms was shown in the nephrogram. Lindblom and Seldinger (1955) described huge avascular malignant renal tumours in 3 out of 16 cases. Olsson and Jönsson (1962) found that abnormal vessels were almost always present with renal tumours, even in the presence of considerable tumour necrosis. They pointed out the importance of a selective angiographic technique to avoid the superimposition of irrelevant vessels. In 1968 Watson, Fleming and Evans found that 6 out of 100 renal carcinomas were "avascular" at arteriography. They emphasised the complementary value of nephrotomograms in showing the shape of intrarenal masses. When a defect in the nephrogram is not clearly round or ovoid but is irregular or poorly defined, a neoplasm should be suspected. Occasionally cysts and tumours may occur together (Rehm, Taylor and Taylor, 1961; Brannan, Miller and Crisler, 1962; Levine, Emmett and Woolner, 1964). Other pathological conditions which have to be considered are a localised multicystic condition which may be present in the upper half of a duplex kidney, and an intrarenal abscess or haematoma particularly in patients having long-term anticoagulant treatment. A renal angiomyolipoma or hamartoma usually shows a characteristic angiographic pattern with small beaded intrarenal vessels or aneurysms (Palmisano, 1967; Wright *et al.*, 1974) but may be avascular.

Case 1: Avascular renal tumour clinically mimicking a renal abscess

A man aged 36 was treated at home for a urinary infection in August 1968. He was given ampicillin and was sufficiently recovered a week later to go camping. A few days later his fever returned and he had dysuria. He was admitted to hospital and again treated with ampicillin. An IVP showed a space-occupying lesion in the left kidney. Because of the fever it was thought likely that he had a renal abscess. The fever subsided and he returned home. A month later he attended hospital in Oxford; at this time there was some tenderness over the left kidney but no mass could be felt. Urine culture yielded a mixed growth of organisms including staphylococci. A further IVP (Fig. 1) again showed evidence of a left renal mass, which was thought possibly to be a residual abscess in the left



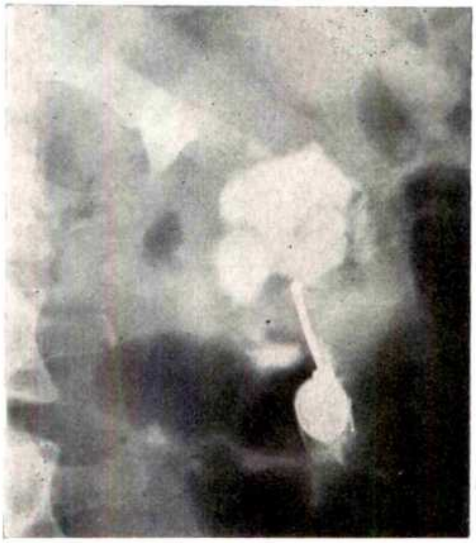


Fig. 1. Case 1. IVP tomogram—mass in the left kidney.

Fig. 2. Case 1. Renal puncture—there is an irregular inner border to the mass and filling defects within it.

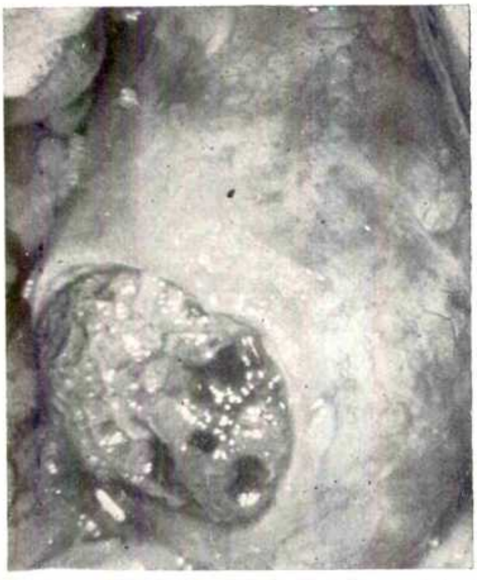
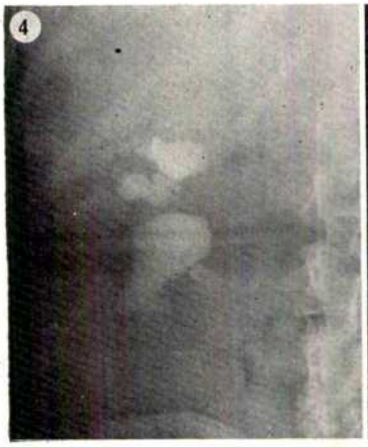


Fig. 3. Case 1. Photograph of the exposed kidney showing the "cyst" opened, its thick wall and debris within it.

kidney. He was admitted to hospital for arteriography; it was planned that if no tumour circulation was seen, a renal puncture should be performed to aspirate the pus and inject the cavity with ampicillin.

The patient was large and rather obese. An aortogram was carried out, with injection of contrast medium into the aorta. No abnormal circulation could be seen either on serial angiogram films or on angiotomograms. A renal puncture was then performed, using a fine lumbar puncture needle. Initially no fluid could be aspirated. Injection of contrast medium showed a large irregular cavity (Fig. 2). Following this, greenish-brown fluid was aspirated which appeared to be altered blood. Microscopy revealed red cells and debris with a few polymorphs and occasional columnar cells. No malignant cells were found. Isotope scintigraphy using a "blood pool" label also failed to show any increased vascularity in the left kidney.



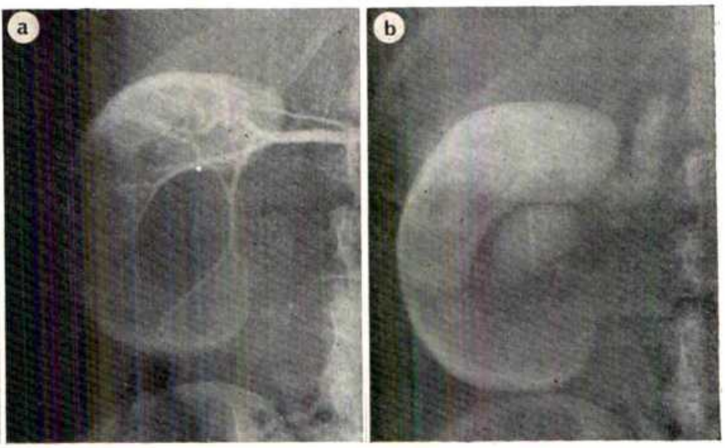


Fig. 4. Case 2. IVP showing the enlarged right kidney and the "giant" calyceal system.

Fig. 5. Case 2. (A) Arterial and (B) nephrogram phases of the selective right renal arteriogram. Note the large "cystic" looking lesion occupying the lower two-thirds of the kidney with a thin rim of functioning renal tissue overlying it. The intrarenal arterial branches appear to be stretched over the mass. The renal vein is clearly shown in the nephrogram phase.

The irregularity of the cavity, the absence of pus and the presence of altered blood suggested a radiological diagnosis of a malignant tumour with a degenerating centre. It appeared that his renal tract infection which led to the tumour being discovered was unrelated to the tumour. A few days later the left kidney was explored and a fluctuant mass was found on its anterior surface (Fig. 3). It was thought it might be a haematoma because of the altered blood. The inner wall was irregular and rough, and frozen section histology showed that within the thickened fibrous tissue of the "cyst" wall there were cells consistent with a papillary adenocarcinoma. The kidney was removed. Histological examination confirmed the presence of papillary adenocarcinoma in the wall of a necrotic and haemorrhagic mass. Mitotic activity was relatively sparse. The surrounding renal tissue showed marked interstitial fibrosis and inflammatory changes with infiltrates of lymphocytes and plasma cells, glomerular atrophy and some periglomerular fibrosis.

He has continued well since the nephrectomy and chest radiographs have shown no evidence of metastases.

Case 2: Avascular renal tumour radiologically mimicking a cyst at selective arteriography

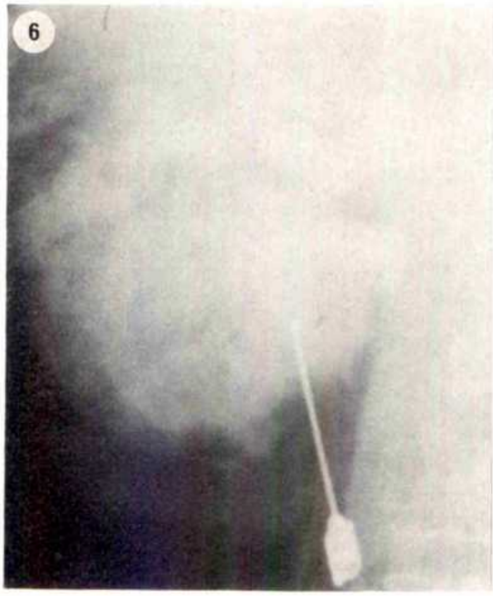
A woman aged 57 developed pain in the right hypochondrium in December 1971 following an upper respiratory infection. She had repeated attacks of vomiting and had been treated with ampicillin and analgesics for a presumed biliary infection.

On admission to hospital in February 1972 a large mass was felt in the right side of the abdomen. It had an irregular edge and there was considerable tenderness over it. She was mildly anaemic (Hb 12·6 g) and had a relative eosinophilia of 11%. An IVP (Fig. 4) showed that the right kidney was enlarged with a generally enlarged calyceal system (as is sometimes seen in association with a hypernephroma). A barium meal showed that the stomach and duodenum were displaced to the left, with a pressure deformity on the 3rd part of the duodenum.

A renal arteriogram showed a large right kidney with a large spherical avascular area in it surrounded by a rim of functioning renal tissue (Fig. 5, A and B). No abnormal vessels were seen, either on serial films taken with the serial changer, or on better quality radiographs taken with the over-couch tube and Bucky. The catheter was removed and the patient turned into the prone position. A renal puncture was performed and greenish-brown fluid was obtained. Injection of contrast medium into the lesion demonstrated a very irregular inner wall (Fig. 6) and appeared to outline debris within it. Examination of the fluid showed that it contained numerous cholesterol crystals. No malignant cells were found.

A transabdominal right nephrectomy was carried out. The tumour appeared to be infiltrating the ascending colon and the third part of the duodenum; a right hemicolectomy was carried out and the third part of the duodenum was partially resected.

Pathological examination showed an encapsulated tumour mass occupying the lower pole. This was 10 cm in diameter, cystic and contained "shaggy" brown material. Histological examination showed that although the greater part of the tumour appeared to be cystic, part of its lining was a papillary carcinoma. The remainder of the kidney appeared normal. In the connective tissue between the renal tumour and the colon there was a massive inflammatory infiltrate composed mainly of lymphocytes tending to be arranged in follicles with some plasma cells and occasional eosinophils. The fibrotic reaction was intense and had produced deeply eosinophilic fibrous tissue,



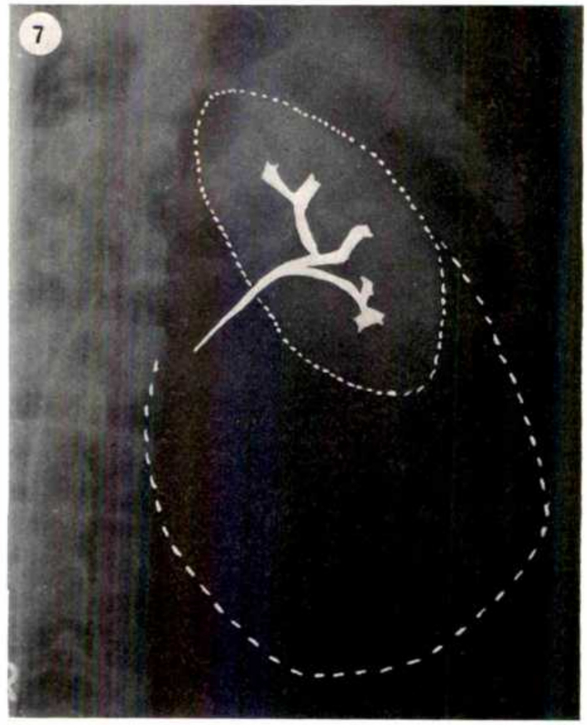


Fig. 6. Case 2. Injection of contrast medium following puncture of the mass, which is shown to have an irregular inner wall and to contain debris.

Fig. 7. Case 3. Nephrogram phase of selective renal arteriogram showing the large "cystic" mass arising from the lower pole of the left kidney and the displacement of the renal pelvis and ureter (retouched figure)

which did not give a positive reaction for amyloid. This inflammatory type of change extended into the wall of the colon and the duodenum. It was thought that to give such a reaction either the "cyst" had burst earlier, or more likely the renal tumour had produced such an intense auto-immune reaction that it became totally sealed off from the rest of the body by the dense fibrous tissue.

Case 3: Large spherical avascular renal tumour mimicking a cyst

A man aged 55 was admitted to hospital in August 1964 with acute left-sided abdominal pain, which started during defecation. On examination he was hypertensive, B.P. 220/105. A large mass was felt in the left side of the abdomen. Initially it was thought that he may have had an acute spontaneous intracapsular rupture of the spleen. His pain settled and he was comfortable in bed. An IVP showed a well-defined spherical soft tissue mass at the lower pole of the left kidney, the calyceal pattern being normal but the lower half of the kidney being tilted laterally. An aortogram and selective left renal angiogram were performed, and no abnormal circulation was seen (Fig. 7). Because it seemed likely that the mass was a cyst, a cyst-puncture was performed. A small amount of contrast medium was introduced to outline the cyst and over 600 ml of brown cyst fluid was aspirated, the discolouration of the fluid presumably being due to old blood. Examination of the fluid revealed large numbers of cholesterol crystals. The "cyst" had a thick wall with an irregular inner border and small filling defects. After 3 months a follow-up IVP showed that the mass was of similar size. It was punctured again with similar findings.

Because of the unusual nature of the lesion the kidney was explored. The mass appeared to be a large cyst arising from the lower pole. It was filled with dark-brown fluid, some of which was inspissated and resembled old pus. It was excised; measured 10 cm in diameter, had a smooth outer surface and contained necrotic-looking material. There were multiple small papillary projections from its inner wall. Histologically it was found to be a papillary adenocarcinoma, with tumour infiltrating the fibrous capsule but not extending through it.

The patient was then re-explored and the remainder of the left kidney was removed. It contained a small residual nodule of tumour, 2 cm in diameter from where the cystic lesion had been excised. The kidney itself showed changes consistent with hypertensive renal disease.

His hypertension needed considerable medical control. He was admitted to hospital twice with myocardial infarctions. He developed diabetes. In June 1970 he died from pulmonary emboli secondary to calf vein thrombosis. The heart showed occlusion of the right coronary artery by organised thrombus and scarring of the posterior wall of the left ventricle. The right kidney was scarred with ischaemic changes. No secondary deposits were found.

Discussion

Because none of these "avascular" renal tumours showed any abnormal vascular pattern, they were dealt with in the same way as in the definitive investigation of renal cysts, *i.e.* by renal puncture, a technique we have used extensively over the past 12 years, and which has recently been reviewed by Jeans, Penry and Roylance (1972). Typically a renal cyst yields clear though slightly yellowish fluid on aspiration, whilst blood or blood-stained fluid is obtained from a hypernephroma. Occasionally blood may be obtained from a cyst into which bleeding has occurred, *e.g.* in polycystic disease. It has also been aspirated from a chronic haematoma in a haemophilic patient. Clear fluid may sometimes be aspirated from the necrotic cavity of a degenerating tumour. The presence of fat in the aspirated fluid has been suggested as a valuable diagnostic feature suggesting the presence of a tumour by Lang (1966) and also in an editorial footnote to a chapter describing the technique of renal puncture (Wright, 1972). Usually, however, the presence of fatty derivatives (*e.g.* cholesterol crystals) in any cyst or tissue fluid is taken as an indication of a benign lesion, but as shown in cases 2 and 3 these may also be found in slowly growing tumours, such as papillary adenocarcinomas or cystadenomas.

Papillary adenocarcinomas or cystadenomas may have a malignant type of circulation or be avascular, as in our 3 cases. Only about 10% of renal pelvis carcinomas show evidence of abnormal vessels at angiography, and hence are usually best examined by retrograde pyelography.

Our cases show that undue reliance of the apparent non-malignant nature of a renal mass must not be placed on arteriography alone. We did not use intra-arterial noradrenaline to try further to demonstrate an abnormal circulation in these patients, as has been used by several authors including Palmisano (1967) and Kahn, Wise and Robbins (1968). Recently Ekelund, Göthlin and Lunderquist (1972) have shown that intra-arterial angiotensin may also increase the diagnostic accuracy of renal angiography, and in 1 illustrated case showed how an apparent cyst had tumour vessels demonstrated marginally in it following its use; however, in 3 cases it did not help.

We believe that when there is a "cystic" or apparently avascular mass in a kidney this should be punctured with a fine (lumbar puncture) needle, and that following the aspiration of a little fluid, contrast medium should be injected to show its contours. Simple cysts have a smooth well-defined inner border, and following aspiration of the cyst fluid (and contrast medium) the kidney morphology will return almost to normal, as can be seen fluoroscopically or on radiographs. With malignant cysts, or cystadenomas, there is a thick irregular inner wall—in addition the mass will not tend to collapse so readily when the fluid is aspirated. A small note of caution is that when ascribing an intrarenal mass entirely to being a simple cyst, one must ensure that it conforms entirely to the size of the renal space-occupying lesion, and if it appears smaller than this then the possibility of another adjacent cyst or tumour must be considered. Similarly, renal puncture or "antegrade" pyelography may be performed when there is an unusual or non-communicating hydronephrosis.

In our cases the definitive diagnostic procedure was the renal puncture with aspiration of the fluid and the demonstration of the irregular inner wall of the "cyst" or hydronephrosis.

Summary

In the past 9 years we have encountered 3 renal space-occupying lesions, which were "avascular" at arteriography but which appeared to be tumours, as shown by renal puncture or "antegrade" pyelography. All had an irregular inner border demonstrated.

The investigation and radiological diagnosis of such masses is discussed and compared with that of renal cysts.

We are indebted to the late Mr A. Elliot Smith and Mr J. C. Smith for access to the case notes of cases 1 and 3 respectively, to Mr B. Higgs and Dr W. B. Thomson for clinical details of case 2 and for referring this case for further investigation. Mr D. Floyd of the Department of Medical Illustration, Radcliffe Infirmary, and Mr R. L. Emanuel, Nuffield Orthopaedic Centre, kindly helped with the illustrations.

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Regression of Metastases after Nephrectomy for Renal Cell Carcinoma

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The rare observation that pulmonary metastases from renal cell carcinoma may regress after removal of the primary neoplasm has prompted many urologists to perform radical nephrectomy in apparently hopeless cases (Gonick and Jackiw, 1964; Garfield and Kennedy, 1972).

Case Report

E. C. (385-03-63-16), a 53-year-old man was admitted with a 1-year history of 30 pound weight loss, anorexia, and generalised weakness. He had one attack of gross, painless haematuria 3 months before admission. Physical examination revealed a large right flank mass. There were no palpable lymph nodes and no other masses. The haematocrit was 42%, the White Blood Count 11,400; urinalysis showed no protein, sugar, WBCs or bacteria, but 7-8 RBCs per HPF. Chest X-ray revealed 5 metastases (Fig. 1).

Total serum protein was 6·3 gm % and albumin 2·1 gm %. Alkaline phosphatase was 183 and 265 m units per ml (upper limit of normal 85 m units per ml). The other liver functions were normal and there was no hypercalcaemia.

Intravenous urography revealed a large right renal mass and angiography demonstrated a large renal cell carcinoma replacing most of the right kidney. On abdominal exploration the tumour was found to be extensively invading perirenal tissue and many enlarged lymph nodes along the aorta and the common bile duct were biopsied. These nodes were not dissected but the kidney and Gerota's fascia were removed intact. Histologic examination of the tumour showed a poorly differentiated and spindle cell carcinoma interspersed with a few areas of the more classical clear cell variety (Fig. 2). The lymph nodes also showed metastatic renal cell carcinoma. The patient's post-operative recovery was unremarkable.

Chest X-ray 1 week after nephrectomy revealed no change. One month later only 2 of the metastases were still recognisable (Fig. 3). We had entertained the idea of starting him on Provera 1 month postoperatively but because of this spontaneous regression, he was not treated. Two months postoperatively only 1 metastasis was identifiable. This one was superimposed on the right hilum and did not change in size throughout this period, nor in the following 5 months (Fig. 4). In addition, the liver functions had all returned to normal and the patient was feeling strong and robust. By 1 year, however, the patient developed new pulmonary and bone metastases.

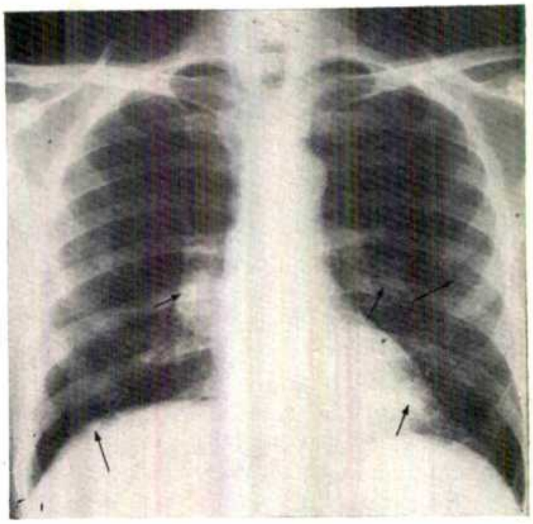


Fig. 1. Preoperative chest X-ray showing 5 metastases of varying size (arrows).

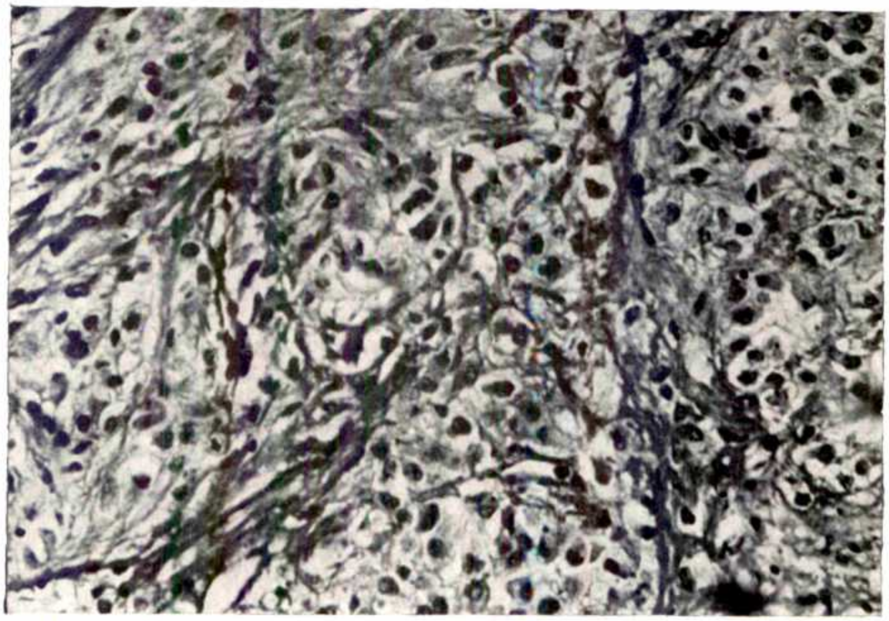


Fig. 2. Histologic section of tumour with poorly differentiated and clear cell carcinoma.

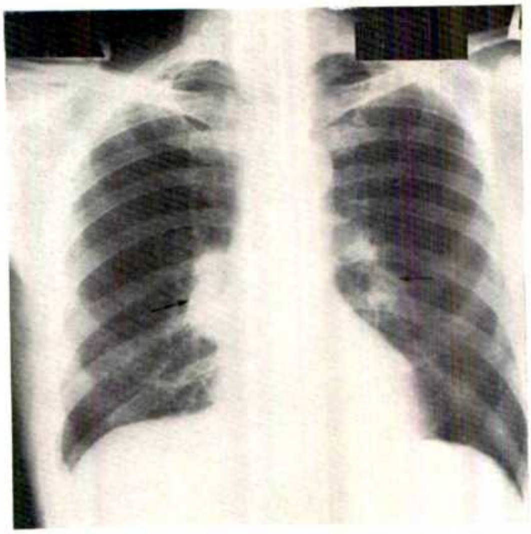
Discussion

There have been only 41 well-documented cases of regression of metastatic lesions from renal cell carcinoma unrelated to hormonal therapy or chemotherapy (Gonick and Jackiw, 1964; Adolfsson, 1966; Everson and Cole, 1966; Markewitz, Taylor and Veenema, 1967; Ridings, 1971; Garfield and Kennedy, 1972). 39 were pulmonary lesions, 30 followed nephrectomy, 2 followed radiation to the primary, 1 regressed spontaneously without nephrectomy and 6 were pulmonary metastases which occurred following nephrectomy and then spontaneously regressed. There has been a case of regression of a bone metastasis and intestinal metastasis (Mims *et al.*, 1966). In 4 cases there was histological proof that the pulmonary coin lesions were indeed neoplasm (Ljungren *et al.*, 1959; Gonick and Jackiw, 1964; Markewitz *et al.*, 1967). In only 1 of these 4 cases however, did the regression of neoplasm directly follow nephrectomy (Markewitz *et al.*, 1967). This patient died 1 year later of new metastases.

Regression is clearly not a common event. Middleton (1967) reported 33 patients with metastatic renal cell carcinoma who underwent nephrectomy without any regression of the metastatic lesions and no survivors after 2 years. The same author reports 45% and 34% 3-year and 5-year survival for nephrectomy and resection of a solitary metastasis. Mims reported 97 patients with metastatic renal cell carcinoma treated by nephrectomy with only 1 case of spontaneous regression of multiple bone metastases (Mims *et al.*, 1966). Their overall 5-year survival rate was 14·6%. Their 1 patient with regression of bone metastases after nephrectomy had a profound lymphocytic reaction surrounding the primary and the authors suggest an immunologic explanation for the regression.

In all the reported cases, regression of metastases was noted by 4 months to 1 year after nephrectomy and could recur in the same or other areas at a later date. Regression was palliative and did not necessarily mean that the patient was cured.

There is a great deal of speculation about the cause of these regressions. By reducing the large amount of tumour antigen in the primary, the host's own immune defences might be able to overcome the remaining tumour. Alternatively, removing the primary might also remove hormonal



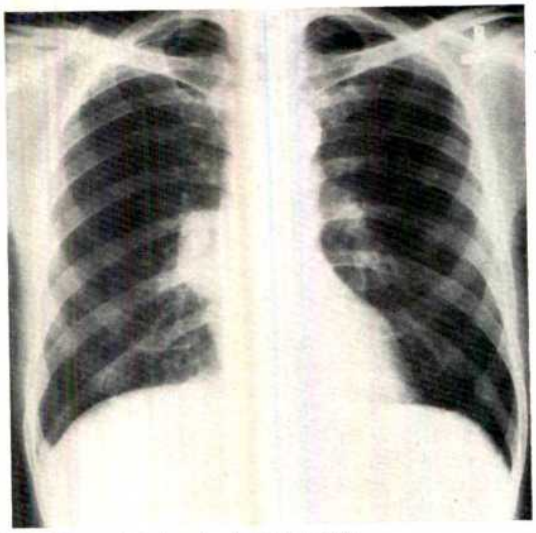


Fig. 3. Chest X-ray 1 month after nephrectomy showing only 2 of the original metastases (arrows).

Fig. 4. Chest X-ray 2 months after nephrectomy showing only the 1 metastasis superimposed on the right hilum. This has not changed in size since the preoperative film.

or other carcinogenic substances released by the primary. A third possibility is that regression is an unpredictable spontaneous event unrelated except by random chance to the nephrectomy.

Studying these rare patients may eventually help us to understand that peculiar balance that exists between the host and his renal cell carcinoma.

Summary

A case of an extensive renal cell carcinoma with temporary regression of pulmonary metastases is reported.

The literature of similar reported cases is briefly reviewed.

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Short Case Report

Delayed Peritoneal-Cutaneous Fistula; a Complication of Bilateral Nephrectomy

A 56-year-old man with end-stage renal disease secondary to polycystic kidneys underwent bilateral nephrectomy on 11th December, 1973, through transperitoneal "chevron" incision. The patient's postoperative course was uneventful until after the second postoperative dialysis, when painful haematomas developed in 3 separate areas of the incision; these were drained, but no later healing was evident (Fig. 1). Suddenly on 10th January 1974, 1 month after surgery, copious amounts of fluid started to leak from a point along the area of breakdown on the right. The leakage of 1 litre of ascitic fluid daily continued for 10 days without any apparent tendency to slow. A sinogram confirmed the presence of a peritoneal-cutaneous fistula (Fig. 2). On 20th January 1974 the wounds and the fistula were excised down to the peritoneum, and primary closure was accomplished. Wound healing occurred uneventfully, although ascites persisted.

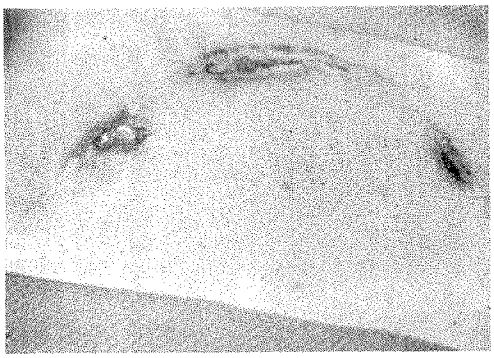

Fig. 1 Areas of breakdown along the incision.

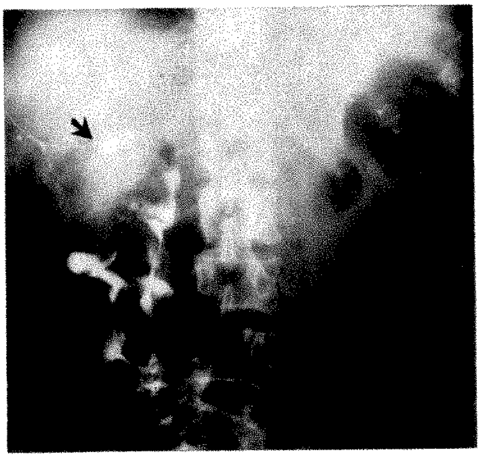

Fig. 2 Arrow points to fistula. Note contrast material in peritoneal cavity.

Comment

The development of a painful wound haematoma may occur during postoperative dialysis and may lead to localised wound breakdown and delayed healing (Wilkinson and Scott, 1970). However, the development of a delayed peritoneal-cutaneous fistula has not been previously reported. The presence of this complication should be suspected when a sudden increase in the amount of drainage appears.

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Ureterometrographic Studies on Human Subjects with Normal Urinary Tract System

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Studies of the basic tone and contractile activity of the ureter and renal pelvis may be employed as a supplementary tool in evaluating the functional state of the urinary conducting system. However, such studies were delayed because of the fear that the presence of a catheter in the ureter would prevent the urine flow and disturb the normal function. The pioneering work of Kiil in 1953 showed that the presence of the ureteral catheter, with its distal end connected to an electromanometer, would not interfere with the urine leakage around the catheter and would cause little physiological alteration.

In this communication, we present ureterometrographic findings obtained from 40 normal subjects.

Materials and Methods

Subjects in whom cystoscopy and/or retrograde pyelography were indicated for one reason or another were submitted to ureterometrographic studies. The recordings from those with negative laboratory, radiographic and cystoscopic findings were taken as normal. Altogether, 40 normal adult subjects, whose age ranged between 17 and 60 years were studied.

Under general or local anaesthesia, a ureteral catheter size 4 or 5F was inserted into the ureter through the cystoscope. The exact location of the proximal end of the catheter was determined by the X-ray. Its distal end was connected to a strain gauge pressure transducer (Statham P23 AC), whose output was fed into the preamplifier unit of a Grass polygraph.

The parameters determined on each subject were as follows: renal pelvis and ureteral resting and contraction pressures, peristaltic frequency, rhythm, shape and contraction-relaxation times. In order to make precise measurement of the latter two, the peristalsis was recorded under different chart speeds. In some cases, recordings were made from different levels of the ureter using X-ray as a guide to the location of the tip of the catheter. The effect of bladder filling on the ureteral peristalsis was studied.

Results

Three representative tracings of normal ureteral motility are presented below (Figs. 1 to 3). They show considerable variations with regard to the frequency, amplitude, rhythm and contraction and relaxation times.

Figure 1 represents the ureteral motility of a 45-year-old non-pregnant woman, in whom the intravenous and retrograde pyelography and bacteriologic study of the urine were normal.

Under constant experimental conditions, recordings were made from the renal pelvis and various segments of the ureter. The frequency of peristalsis was 5 waves per minute, and remained so at different sites of recording. The contraction pressure was least in the renal pelvis—4 to 6 cm

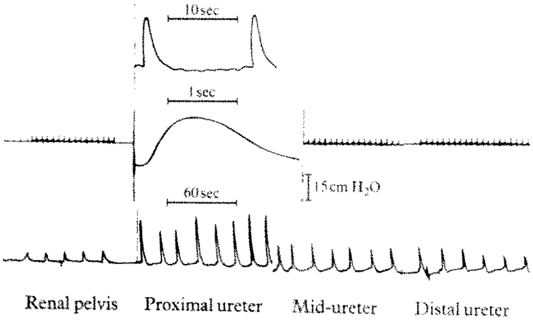

Fig. 1. Renal pelvic and ureteral peristalsis in a 45-year-old woman with normal urinary tract system. Note that the upper ureteral motility was recorded under different speeds of the moving paper.

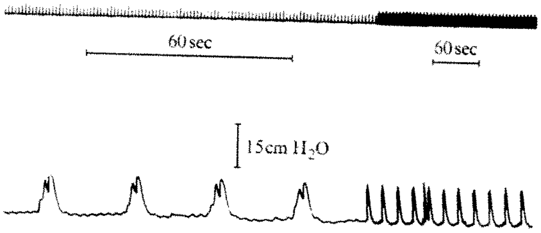

Fig. 2. The mid ureteral peristalsis in a 26-year-old man. Note the presence of the notch on the contraction part of the peristalsis.

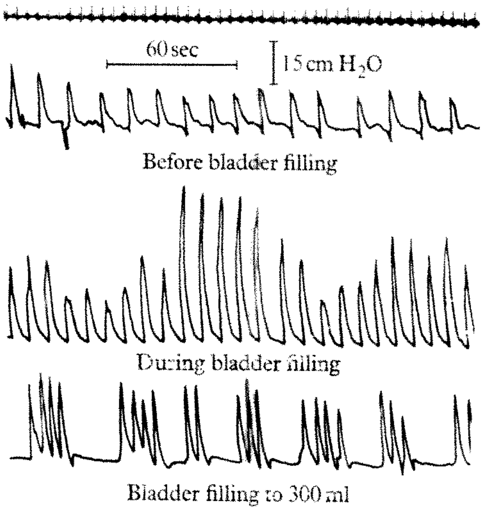

Fig. 3. Effect of retrograde filling of the bladder with normal saline on the ureteral motility.

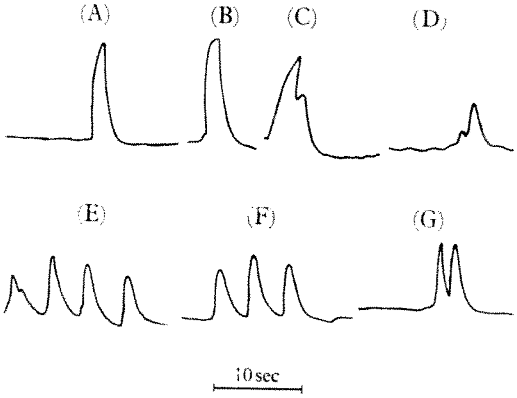

Fig. 4. Various shapes of ureteral peristalsis recorded from different individuals. Tracings E and F were recorded from the same subject, representing quadrigeminy and trigeminy respectively. Tracing G shows bigeminy. The latter 3 patterns appeared occasionally while the main form was monophasic peristaltic complexes.

H_2O; and highest in the upper ureter—20 to 28 cm H_2O. The contraction time of the peristaltic wave was 0·8 second, and the relaxation time lasted 1·4 seconds (Fig. 1, middle tracing). The rhythm was fairly regular.

Figure 2 is the tracing of the mid ureteral peristalsis in a 26-year-old man. The peristaltic frequency was 3 waves per minute, with regular rhythm and an amplitude of 12 cm H_2O. The shape was characterised by notched peristaltic complexes. The contraction-relaxation time lasted 7 seconds.

Figure 3 shows the effect of bladder filling on ureteral motility in a 35-year-old woman with normal urinary tract system. A Foley catheter number F12 was positioned in the bladder. Ureteral motility was recorded prior to and during the bladder filling. The pre-filling recording showed a frequency of 6 waves/minute with a pressure of 8 to 17 cm H_2O with fairly regular rhythm.

During bladder filling with normal saline, the ureter appeared to be more active. Frequency increased to 7 waves/minute. The maximum pressure was now 47 cm H_20. When the bladder was distended up to 300 ml, there were quadrigeminy, trigeminy and bigeminy waves, appearing at irregular intervals. Similar results were observed in 4 other subjects in whom bladder filling was performed to the same extent.

Generally in individual recordings, the *frequency* of the contractions was the same in the renal pelvis, and upper, middle, and lower ureter if recording from these various parts succeeded each other quickly, to minimise the effect of time lapse on the rate of the peristaltic waves.

The *contraction pressure* of the upper ureter (20 to 44 cm H_20) was greater than that of the mid ureter (10 to 37 cm H_20), and the contraction pressure of the latter was greater than that of the lower ureter (6 to 30 cm H_20). The pelvic contraction pressure was the least (3 to 10 cm H_20).

The *resting pressure* was highest in the renal pelvis (1·5 to 9 cm H_20) and decreased gradually down the ureteric channel.

In most subjects, the *ureteral contraction complexes* were monophasic; an ascending limb followed by a descending branch (Fig. 4, A, B). Some normal recordings had a notch either in the ascending (Fig. 4, D) or descending portion (Fig. 4, C). In some cases, patterns of diphasic waves were recorded characterised by an incomplete contraction superimposed by another contraction. In general no particular pattern could be attributed to a special portion of the ureter although Weinberg and Maletta (1961) recorded diphasic waves from the lower ureter only.

Table I presents the parameters of the mid-ureteral peristalsis of the 40 subjects studied.

Table I

Characteristics of Normal Motility as Recorded from the Mid Ureter

Parameters	Average	Range
Frequency	4 Waves/min	3–6 Waves/min
Pressure	16 cm H_2O	10–37 cm H_2O
Contraction Time	1·8 sec	1–3 sec
Relaxation Time	1·7 sec	1·4–3·5 sec
Resting Pressure	2·5 cm H_2O	0–7·5 cm H_20

Discussion

Little is yet known about the normal physiology of the ureter and renal pelvis. While extensive work has been done on other smooth muscle-containing organs, the study on the ureter has been comparatively small.

Propagation of urine from the renal pelvis toward the bladder, to some extent, is accomplished by the rhythmic contractions of the smooth muscle of the ureter.

The average contraction pressures recorded from the upper, mid, and lower ureter were 20, 16, and 10 cm water respectively.

Thus the contraction pressure was highest in the upper ureter and least in the lower ureter. This finding is in agreement with those of Ross *et al.* (1967), but it differs from the data obtained by Lapides (1948), Auvert (1957) and Orkin (1964) who found that the pressure amplitude increased as the contraction waves approached the bladder.

The average frequency of ureteral contractions was 4 waves/minute with a range of 3 to 6 waves/minute. These values are close to those reported by Ross *et al.* (1967), and Edmond, Ross and Kirkland (1970) who found the rate of ureteral peristalsis to be 2 to 4 waves/minute and 2 to 6 waves/minute respectively. The ureteral peristaltic frequency compares well with that of other smooth muscle-containing organs such as stomach (3 waves/minute) and duodenum (7 to 8 waves/minute), (Davenport, 1961).

No difference was noted between the ureteral peristaltic rate and that of the renal pelvis in the same individual. This is in contrast to the findings of Murnaghan (1959)and Edmond *et al.*(1970), who recorded more frequent peristaltic activity from the renal pelvis.

Absolute regularity of the rhythm characterised by equal time intervals between 2 contraction waves as seen for example in the normal electrocardiogram was not observed; the degree of irregularity seemed to be influenced by the length of the experiment.

The range of the total contraction and relaxation times together was 2·4 to 6·5 seconds. The reported systolic and diastolic time in literature is 7 seconds (Ross *et al.*, 1967; Edmond *et al.*, 1970).

The contraction-relaxation time of osophagus lasts 3 to 7 seconds (Davenport, 1961), the cardiac cycle (systole and diastole) lasts 0·6 to 1 second and the twitch time of fast skeletal muscle is 10 milliseconds or less, while in the slow skeletal muscle, it lasts 100 milliseconds or more (Guyton, 1971). Table II compares the contraction-relaxation time of various muscles of different organs.

Table II

Contraction and Relaxation Time of Various Muscles

Muscle	Time
Ureteral	2·4–6·5 seconds
Oesophageal	3–7 seconds
Cardiac	0·6–1 second
Slow Skeletal	≧100 milliseconds
Fast Skeletal	≦10 milliseconds

Two more points have to be discussed. One is in relation to the diagnostic value of notched complexes in obstructive uropathies, as claimed by Ensor, Boyarsky and Glenn (1967). Although we do not dispute the validity of the claim, our results showed that the presence of notched complexes does not necessarily indicate ureteral obstruction. The second point regards the effect of bladder filling on the ureteral motility. Davis and Zimskind (1963) demonstrated that if intravesical pressure is raised sufficiently, ureteral peristalsis is abolished. We did not intend to overdistend the bladder beyond its physiologic limits, rather, we produced a normal condition by filling the bladder to 300 ml. Ureteral peristalsis not only did not disappear, but in fact contraction pressure increased in amplitude. Furthermore, bigeminy, trigeminy and quadrigeminy developed as well, suggesting a state of hyperactivity presumably because of increased intravesical pressure causing increased resistance to downstream flow.

Summary

Ureteral motility was studied in 40 subjects with normal urinary tract systems.

Although the contraction waves were often monophasic in shape some were characterised by the presence of a notch on the contraction or relaxation limb of the peristaltic complex, indicating that notched complexes do not necessarily signify obstructive uropathy.

Retrograde filling of the bladder to within its physiologic limits with isotonic saline solution markedly changed the pattern of the ureteral activity.

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Short Case Report

Cystic Nephroblastoma in an Adult

A 77-year-old woman was admitted with an abdominal mass, dull right-sided abdominal pain, loss of weight and anorexia of about 18 months' duration. There were no urinary symptoms. Abdominal examination revealed an ovoid firm mass in the right lumbar region measuring 15 cm in its longest vertical diameter. It was mobile, ballotable and not tender. The pyelogram was normal, but a soft tissue shadow on the outer and lower aspects of the right kidney was found.

Laparotomy revealed a large retroperitoneal tumour arising from the lower outer convex border of the right kidney. Nearly 90% of the kidney looked normal. There were no secondary deposits, and after a total nephrectomy the patient made a satisfactory recovery and was discharged on the 21st postoperative day.

The tumour measured 12 × 12 × 10 cm and had a smooth surface. It was attached to the lower pole of the kidney which looked normal and was sharply defined from the tumour. It consisted mainly of cysts varying from $\frac{1}{2}$ to 3 cm in diameter. They did not communicate with the pelvis (Fig. 1).

Microscopically the renal tissue was normal. The tumour consisted of solid parts and cysts lined with cuboidal and flattened epithelium. The solid parts contained tubules in various stages of development in a stroma of round, spindle and undifferentiated cells (Fig. 2). Some of the tubules were tortuous and invaginated by tufts of stromal tissue giving the appearance of abortive embryonic glomeruli (Fig. 3).

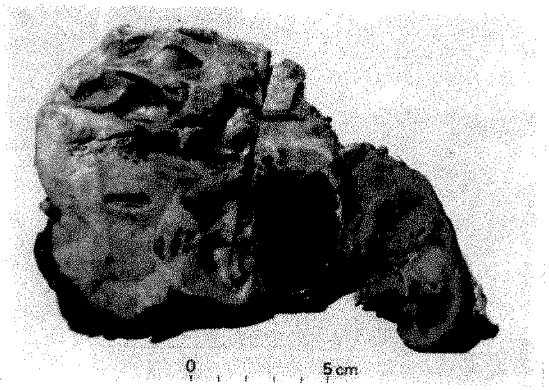

Fig. 1

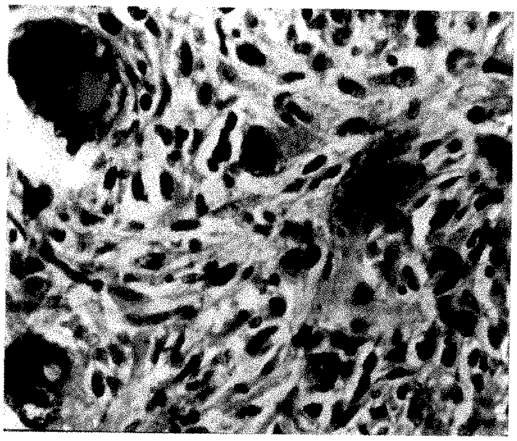

Fig. 2

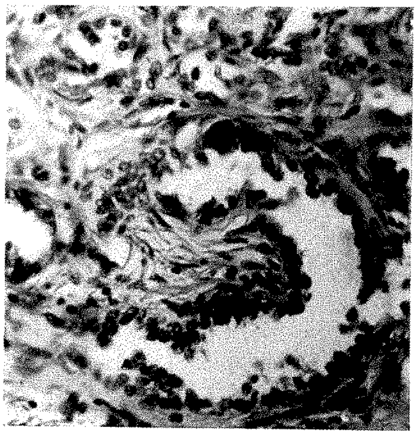

Fig. 3

Comment

The rarity of nephroblastomas in adults is well known, and the most recent review is that of Olsen and Bischoff (1970). The association of nephroblastoma and multilocular cyst of the kidney was described by Christ (1967) and the literature is reviewed by Fowler (1971).

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Urinary Diversion: the Physiological Rationale for Non-refluxing Colonic Conduits

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The desirability and necessity of providing patients undergoing urinary diversion with a suitable and practical means of eliminating urine has long taxed the imagination of urologists, especially since the advent of major ablative cancer surgery. Transplantation of the ureters into the intact sigmoid with incorporation of a valve-like mechanism was first performed by Mayo and Coffey in 1912 and described by Coffey (1928). A wide variety of ureteral anastomoses into the intact sigmoid was subsequently described, and the popularity of ureterosigmoidostomy increased substantially over the next 40 years. However, not until Ferris and Odel (1950) reported on the problems of electrolyte imbalance in these patients was a critical re-evaluation of the problem of urinary diversion undertaken.

Since Bricker (1950) popularised the use of an isolated segment of ileum, the ileal loop has largely replaced ureterosigmoidostomy as a bladder substitute. As long-term follow-up data have become available, however, delayed complications resulting from this form of diversion have become increasingly apparent.

Mogg (1965) redirected attention to the use of a segment of sigmoid colon as an isolated conduit rather than in continuity with the faecal stream. Whereas Mogg's group made little effort to create an antirefluxing uretero-intestinal anastomosis, Leadbetter and Clarke (1955) have clearly shown that this is possible, and the long-term advantage of this alone may prevent the late serious complications of pyelonephritis and calculus formation seen with ileal loops.

Recent studies have compared ileal and colonic conduits in man; however, individual differences in position, acid-base and electrolyte balance, intra-abdominal pressure, and state of hydration make adequate comparison difficult. In order to minimise the number of variables, this study was formulated to compare both small and large bowel conduits in the same experimental animal by creating an ileal conduit from the right kidney and a non-refluxing colonic conduit from the left kidney (Fig. 1). In addition, this study made possible further evaluation in the dog of the basic physiology of sigmoid loops with tunneled ureters vis-à-vis the traditional ileal loop form of diversion.

Materials and Method

16 adult mongrel dogs with normal preoperative creatinine levels and sterile urine cultures were used. After intravenous administration of pentobarbital and a midline incision, 10-cm segments of colon, distal ileum, or both, were isolated, and entero-enterostomy was performed with a two-layer silk anastomosis. The proximal ends of the conduits were closed with inverting two-layer chromic (Parker-Kerr) suture, followed by an interrupted silk layer. All uretero-colonic anastomoses were of the tunneled (3-cm) mucosa-to-mucosa type, as described by Leadbetter and Clarke (1955). All uretero-ileal anastomoses were direct one-layer interrupted mucosa-to-mucosa type without stents. All the conduits were made isoperistaltic. Stomas 2–3 cm in diameter were created for all loops. Antibiotics were administered routinely for 3 days postoperatively. In 5 of these dogs, only 1 kidney was implanted in a loop (3 colonic and 2 ileal); the other kidney remained in continuity with the bladder and thus served as a control.

Intravenous pyelograms were obtained at 1 and 3 months postoperatively. Conduitograms were obtained at 6 weeks postoperatively with a 16F Foley catheter and gravity filling (35 cm H_2O). Pressure tracings were taken with

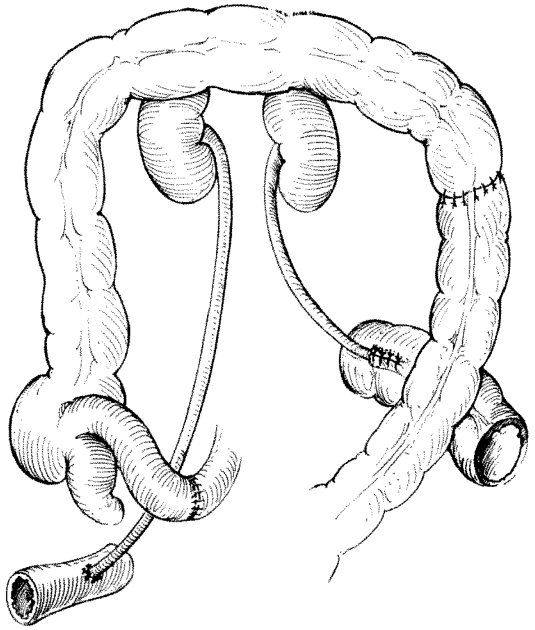


Fig. 1. Schematic drawing of experimental preparation. Right kidney is connected to ileal conduit and left kidney to tunnelled colonic conduit in the dog.

the Sanborn Polygraph (Model 7702B) connected to Statham strain gauges (0–75 cm Hg). Simultaneous tracings were done in unoccluded loops with 8F plastic feeding catheters and in occluded loops with 16F Foley catheters. After acute occlusion, pressures were recorded simultaneously as saline was introduced into the loops in proportion to the capacity. Functional emptying of the conduits was evaluated by the introduction of Technetium-99m-diethyltriaminopentacetic acid (^{99m}Tc-DTPA) until capacity was reached; serial collections of urinary efflux were collected every 15 minutes and emptying curves charted. Serum creatinine levels were measured at 1 and 3 months postoperatively, and blood and urine specimens were analysed for pH and bicarbonate.

All dogs were sacrificed at 3 months postoperatively. Urine cultures were collected at necropsy from conduits, bladder (by needle aspiration), or both, and from both renal pelves. Histologic sections of both kidneys and ureters were taken.

Results

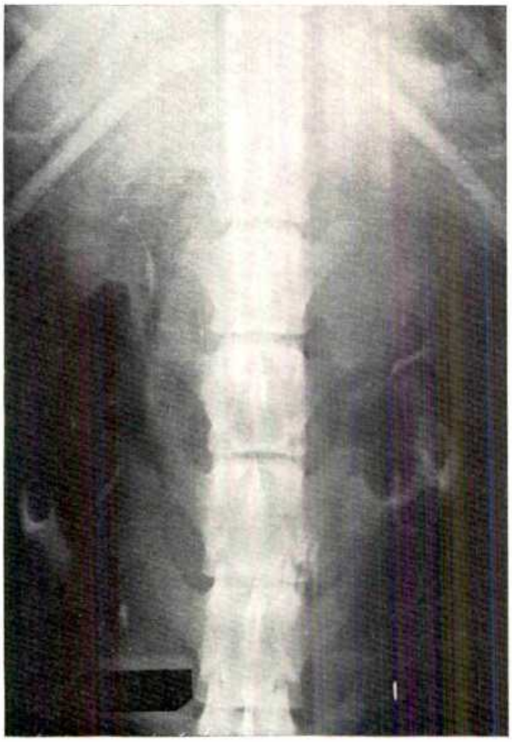
15 of the 16 dogs were available for a 3-month follow-up study. One dog among the control group died of wound infection and sepsis. Three instances of stomal stenosis, all occurring in ileal conduits, required surgical revision at 1 month. There were no urine leaks, no intestinal obstructions, and no ureterointestinal obstructions.

Radiological Studies

Intravenous pyelograms performed at 3 months were normal in all dogs (Fig. 2); 3 with stomal stenosis at 1 month had 2+ dilatation of the right renal pelvis which returned to normal after revision. Conduitograms using equal gravity filling showed free reflux in 11 of the 12 ileal loops and absence of reflux in all 14 colonic loops (Fig. 3).

Chemistry Studies

All serum creatinine levels were normal at 3 months postoperatively, and there were no instances of elevated serum chloride or lowered bicarbonate. Urinary pH collected from both loops or from one loop and bladder showed no significant differences (6·0–6·4), and bicarbonate excretion in all loops was zero.



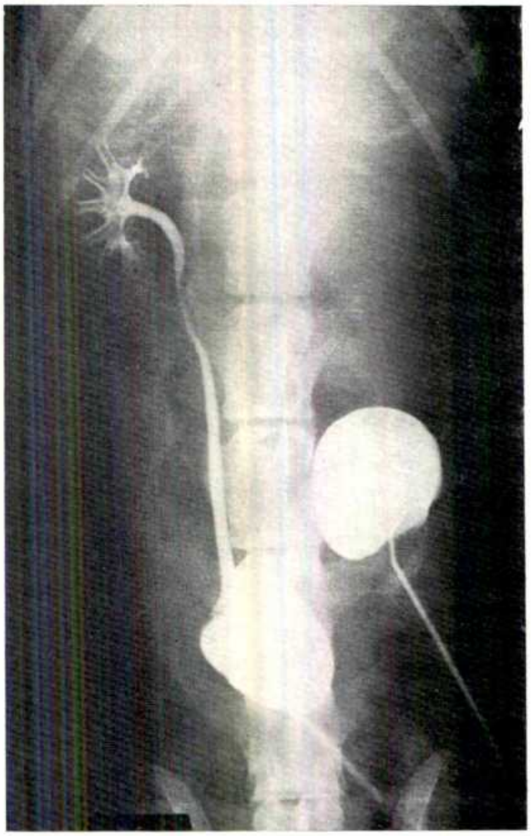


Fig. 2. Dog No. 10 with right ileal and left colonic loops. Normal IVP 3 months after diversion.

Fig. 3. Dog No. 7. Conduitogram demonstrates free reflux in ileal conduit (right) and absence of reflux in colonic conduit (left).

Conduit Dynamics

Emptying curves showed essentially no difference between colonic and ileal conduits (Fig. 4). Resting pressures were uniformly low in both conduits, averaging 3–4 mm Hg. Peristaltic waves occurred more frequently in ileal conduits, and pressure spikes were higher. After acute occlusion, pressures were elevated more rapidly in the ileum with higher pressure spikes (Fig. 5).

Histology

Histologic evidence of pyelonephritis was present in 83% of kidneys connected to ileal conduits, as compared to 7% of those connected to colonic conduits ($P < 0{\cdot}001$). Ten of the 12 "ileal" kidneys demonstrated focal areas of chronic fibrosis and glomerular atrophy in association with acute and chronic pyelitis (Fig. 6, A and B). Eleven of the 14 "colonic" kidneys were histologically normal, as were all the control kidneys.

Bacteriology

Significant bacterial growth was present in 57% of colonic and 50% of ileal conduits. Although ureters connected to colonic conduits had fewer positive cultures than those connected to ileal conduits, the difference was not statistically significant. No correlation was demonstrated between the histologic findings and infection (Table I).

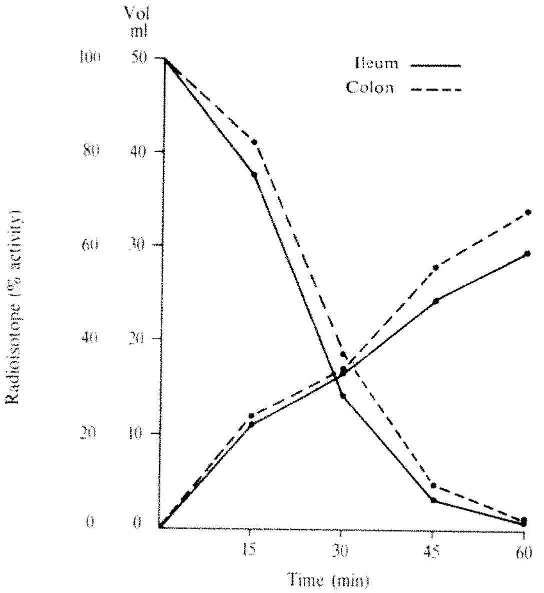


Fig. 4. Dog No. 7. Emptying curves of ileal and colonic conduits using ^{99m}Tc-DTPA.

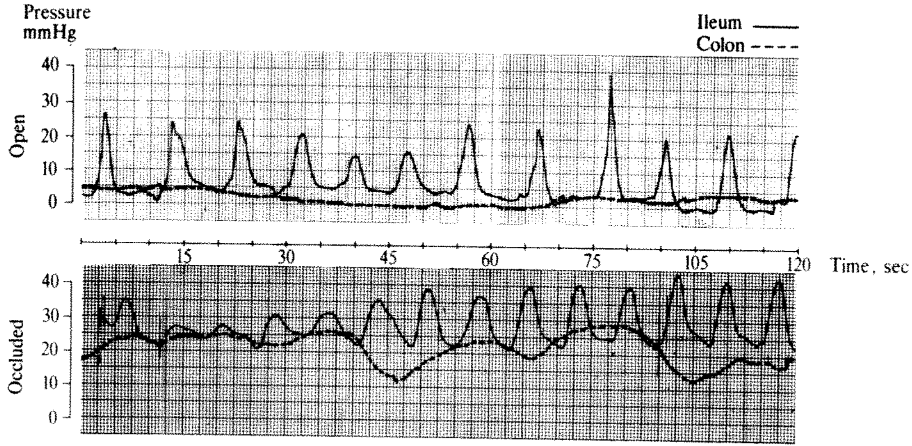


Fig. 5. Dog No. 12. Comparison of simultaneous pressure tracings in open and occluded conduits. Note the more frequent and higher pressures in ileal conduits.

Discussion

That ureterosigmoidostomy was used for more than 4 decades before its deleterious effects were noted should serve as a warning that caution is imperative in the evaluation of any new form of diversion. Although ileal loop diversion has been used successfully for the past 20 years, long-term evaluation has revealed a high rate of delayed complications. Murphy and Schoenberg (1967) reported an incidence of deterioration of renal function in 22% and calculus formation in 12% of 54 patients followed for 4 to 14 years. Koehler, Bowles and McAlister (1967) evaluated 43 patients followed for 5·5 years and found deterioration in 20% and calculi in 24%. Smith (1972) reported no instances of renal calculi but noted a deterioration of 10% in children with normal intravenous urograms preoperatively. This amount of deterioration is even more striking

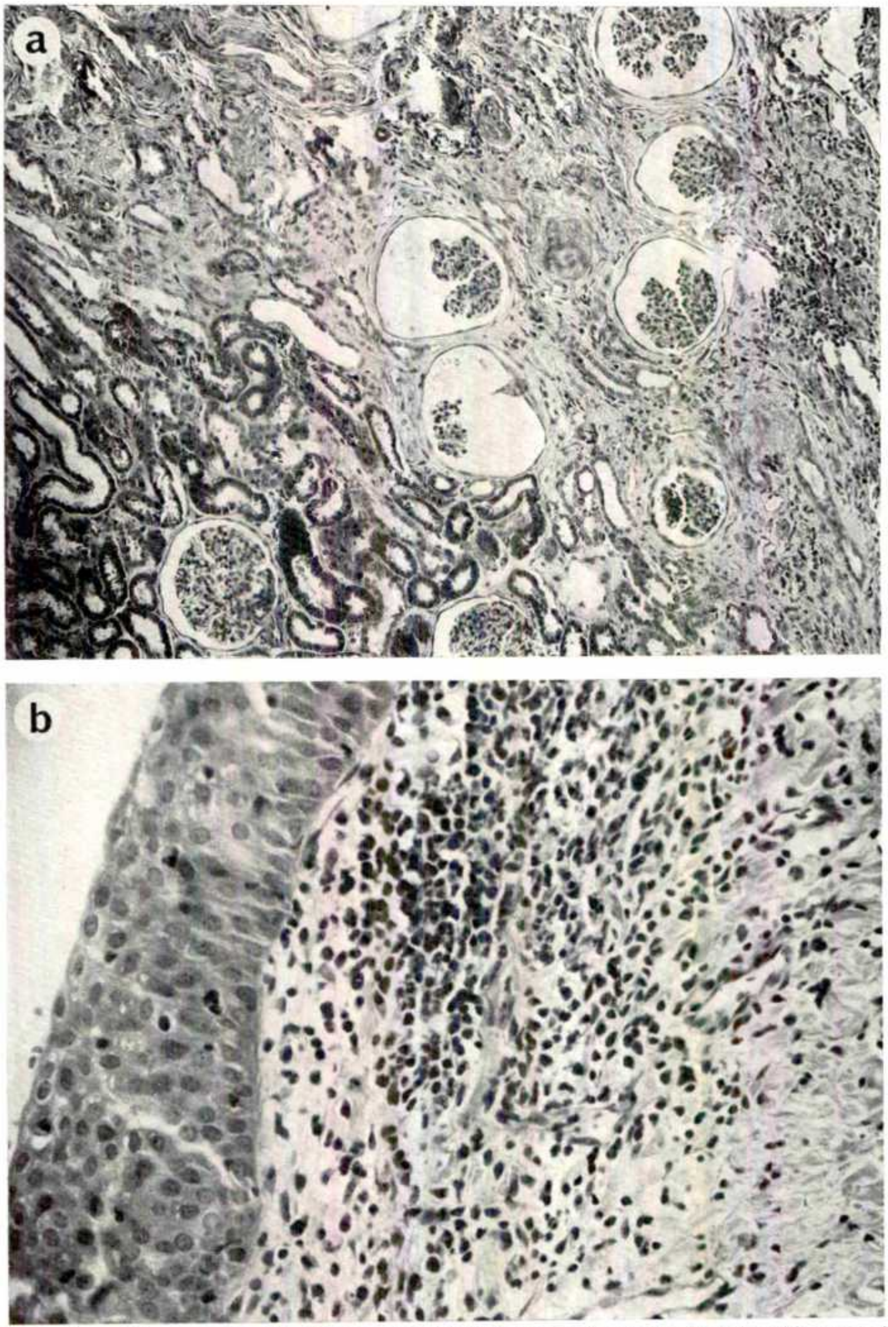


Fig. 6. A, Cortex from kidney connected to ileal conduit. Normal area at lower left. (H & E × 40). **B**, Section of rena pelvis from same kidney. Note thickening of transitional epithelium and chronic inflammatory infiltrate. (H & E × 100.)

Table I

Correlation of Histologic Findings with Infection in Colonic and Ileal Conduits

		Ureteral Urine Culture		Conduit Urine Culture	
Histopathology		$< 10^5$	$> 10^5$	$< 10^5$	$> 10^5$
Colonic Conduits	(14 kidneys)				
Pyelonephritis	(1)	1	0	1	0
Pyelitis	(2)	1	1	1	1
Normal	(11)	7	4	4	7
		9	5	6	8
Ileal Conduits	(12 kidneys)				
Pyelonephritis	(10)	4	6	5	5
Pyelitis	(1)	0	1	0	1
Normal	(1)	1*	0	1	0
		5	7	6	6

*No Growth

when one considers that average follow-up periods are less than 5 years. Although stomal or uretero-ileal obstructions are obvious causes for deterioration, in many patients no aetiology can be found.

Most of the current ileal loop operations employ a direct mucosa-to-mucosa uretero-ileal anastomosis that allows for free reflux of urine from the ileal segment to the upper tracts. Almost all patients with ileal loops have bacteriuria, but the incidence of silent but progressive pyelonephritis in these patients will only become apparent with time. Constant bacteriuria with reflux will remain a continued hazard to renal function.

The use of ileum has led to frequent stomal problems, especially in children. Most series report an incidence of stomal stenosis requiring at least one revision in 25% of cases (Retik, Perlmutter and Gross, 1967; Cordonnier, 1968; Ray and De Domenico, 1972). Because of its larger diameter, the colon is better suited for a cutaneous stoma. In our series, stenosis occurred in 25% of ileal stomas; no stenosis was noted in the colonic stomas.

After studying pressures in colonic and ileal conduits in patients, Dybner, Jeter and Lattimer (1972) concluded that resting pressures are higher in colonic conduits. Our study, utilising a preparation designed to obviate differences in factors such as position and intra-abdominal pressure, has shown no difference in resting pressures. Furthermore, colonic segments have a more blunted response to acute occlusion.

Although the phenomenon of hyperchloremic acidosis has been associated primarily with ureterosigmoidostomy employing the intact colon, Heidenhain (1894) and Goldschmidt and Dayton (1919) demonstrated that ileal segments actively absorb sodium and chloride and excrete bicarbonate. They also showed that sodium and chloride absorption from the colon was far less per unit of measured surface than from the ileum. When either segment is used as a conduit rather than as a reservoir, hyperchloremic acidosis is seldom a problem. We have encountered no instances of electrolyte imbalance in this series.

Spence, Esho and Cass (1972) have documented the development of pyelonephritis at 3 months in 67% of dogs with freely refluxing colonic conduits. In our series at 3 months, pyelonephritis was seen in 83·3% of dogs with freely refluxing ileal conduits, whereas in dogs with non-refluxing colonic conduits, it occurred in only 7·1% ($P < 0{\cdot}001$).

Use of an antirefluxing uretero-colonic anastomosis could be advantageous in those patients in whom the sigmoid segment is considered a total but temporary diversion while reconstructive procedures are being performed on the bladder. Subsequently, when the sigmoid segment is anastomosed to the bladder, the upper tracts remain protected from the high bladder pressures by the antireflux mechanism.

Colonic conduits offer major theoretical advantages over ileal conduits. In patients who require diversion for benign disease, life expectancy is dependent upon preservation of renal function. The prevention of infected reflux, with the consequent decrease in pyelonephritis, would seem to offer a clear-cut advantage.

Summary

In order to make an accurate comparison between ileal and colonic conduits, an ileal conduit was created from one kidney and a non-refluxing colonic conduit from the other kidney in 16 adult mongrel dogs.

Colonic loops do not reflux, have equal resting pressures and rate of emptying when contrasted with ileal conduits, and carry a lower incidence of stomal complications. Colonic conduits respond more favourably to acute occlusion and produce a significantly lower rate of pyelonephritis at 3 months.

These factors suggest that colonic conduits offer a definite advantage for long-term urinary diversion.

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Short Case Report

A Rare Ureteral Injury Secondary to Lumbar Sympathetic Ganglion Block with Phenol

A 58-year-old white male presented with pain, temperature (101 °F), and a mass in the left lower quadrant of the abdomen for 8 to 10 days. One month and 5 months before admission he twice underwent left-sided lumbar sympathetic ganglion block with 8 ml of 5% phenol for Buerger's disease. Intravenous pyelography revealed a normal right kidney but grade 2 pyelocalyectasis on the left (Fig. 1). Retrograde pyelogram was diagnostic of left ureteral injury and retroperitoneal urinary extravasation (Fig. 2).

Through a left-flank incision the uroma was drained and a nephrostomy tube inserted. The patient was discharged from the hospital on the 10th day to come later for ureteral reconstruction. However, he returned a few days later since the nephrostomy tube accidently slipped out, causing alarming haemorrhage. This necessitated emergency nephrectomy and the patient had a smooth postoperative course.

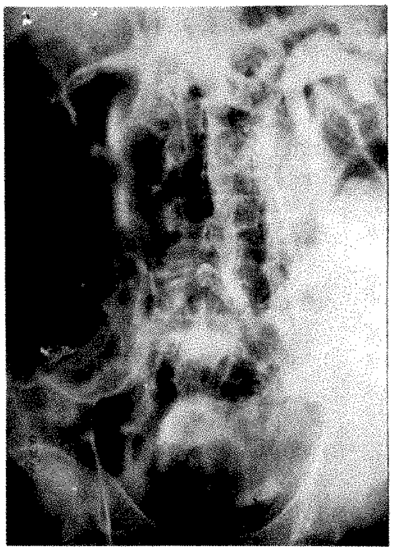

Fig. 1

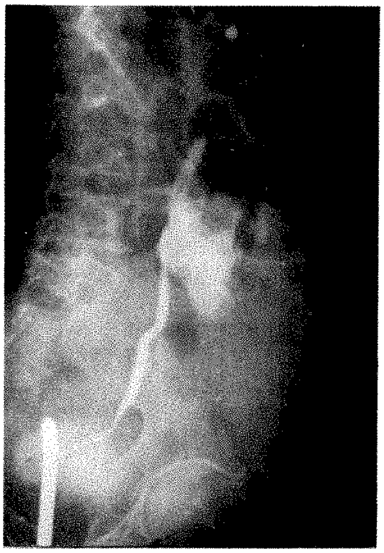

Fig. 2

Comment

Ureteral injury has been reported in gynaecological, colorectal and urological surgery. It is a known complication of ureteral catheterisation and stone manipulation. Ureteral injury during lumbar disc operations is rare, but still rarer in the author's opinion is the present case. Presumably phenol was deposited on the ureter or in its vicinity causing necrosis of the ureter.

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Whole Body Potassium in Patients with Uretero-sigmoid Anastomoses

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Biochemical changes following ureterocolic anastomosis usually include elevation of the plasma concentrations of hydrogen ion (Jacobs and Stirling, 1952), chloride and urea (Ferris and Odel, 1950; Doroshow, 1951; Wilkinson, 1952). Concomitantly, the plasma concentrations of bicarbonate (Ferris and Odel, 1950) and, less commonly, of potassium (Wilkinson, 1952; Garrett and Mertz, 1954) are reduced. The development of striated muscle paralysis, apparently due to potassium depletion (Loughlin, 1956), is not unusual if the hyperchloraemic acidosis is left untreated (Wakim, 1970). Skanse and Widén (1955) considered the muscular paresis associated with ureterocolic anastomosis to result from hypokalaemia. However, the plasma concentration of potassium is not a reliable indicator of the total body content or of the physiological status of the patient in respect of this cation.

When urine collection is rendered impracticable by the ureterocolonic urinary diversion procedure, the validity of measuring exchangeable potassium by the conventional ^{42}K isotope dilution technique is questionable although the method has been used (Ansell, Geist and Creevy, 1961). Whole body monitoring has therefore been utilised to provide direct measurements of total body potassium in such patients in the present investigation.

Patients and Methods

Eleven patients, 10 males and 1 female, age range 52 to 66 years, were studied (Table I). All except 1 elderly man (no. 7) were active and ambulant. All patients had undergone cystectomy 4 months to 13 years (mean 4 years) previously and had bilateral uretero-sigmoid anastomoses. Three of the patients were being treated at the time of measurement with oral potassium supplements (30 to 46 mEq potassium daily given as "Slow-K"). Two were taking potassium supplements as a complement to diuretic therapy for congestive heart failure and the other was the elderly patient, no. 7, who was so accustomed to potassium therapy he did not wish to stop the familiar tablets. All patients had received alkali therapy routinely since their operations, initially with sodium bicarbonate and/or sodium or potassium citrate. During the 3 years prior to the measurement of total body potassium, alkali therapy was rationalised and intensified. In principle, all patients during these years were treated with Shohl's mixture (essentially sodium citrate providing 1 mEq alkali per ml) in doses ranging between 90 and 150 ml per day (Table II). Thus for individual periods ranging between 10 months and 3 years prior to the measurement of total body potassium, all patients except one had been maintained in acid-base balance (*i.e.*, capillary blood pH 7·38 to 7·42, plasma total bicarbonate 24 to 28 mEq/l, base deficit or excess within ±3 of zero). The exception was the female patient whose operation was undertaken only 4 months prior to measurement, and who was still being inadequately treated with potassium supplements and diuretics, on account of incipient congestive heart failure. In general, when alkali therapy was adequate, potassium supplements were not required to maintain satisfactory plasma potassium levels.

Table I

Potassium data, skinfold thicknesses and lean body mass in patients with uretero-sigmoid anastomoses

Patient No.	Age yr	Wt kg	Ht cm	Plasma K mEq/l	Measured TBK mEq	Estimated TBK		Skinfold thickness (mm)		Lean body mass (% body weight)		TBK/LBM mEq/kg
						mEq ± σ (1)	mEq ± σ (2)	Triceps	Subscapular	TBK**	SFT‡	
1	52	46·2	162·6	4·7	2645	2432 ± 274	2808 ± 337	4·2	5·4	100	89	64·4
2	53	66·4	174·7	4·7	3660	3330 ± 268	3440 ± 339	8·7	14·2	84	76	72·5
3	54	87·5	174·0	4·1	3166	3798 ± 277	3394 ± 340	15·3	22·6	59	68	53·2
4	56	65·9	156·2	4·0	3113	2632 ± 275	2430 ± 346	17·3	24·0	78	67	70·4
5	59	71·4	168·9	5·0	3118	3161 ± 270	3066 ± 342	7·7	22·1	72	72	60·7
6	63	74·6	171·5	3·8	2844	3292 ± 274	3174 ± 347	11·5	12·9	66	75	50·8
7	63	39·6	154·9	5·3	2368	1870 ± 287	2294 ± 351	3·3	8·0	100	87	68·6
8	64	80·3	174·0	3·5	3665	3504 ± 279	3297 ± 351	8·4	15·7	69	75	60·9
9	66	52·5	157·5	5·9	2609	2235 ± 277	2402 ± 349	8·4	15·5	91	76	65·4
10	72	88·0	174·0	3·7	3253	3593 ± 294	3220 ± 364	11·5	22·8	60	70	52·8
11F	58	57·9	153·7	4·0	1926	2043 ± 199	1985 ± 225	18·4	21·7	65	63	52·8

Key: F = Female
(1) = Regression using patient's height, age *and* weight (Boddy *et al.*, 1972)
(2) = Regression using patient's height and age only (Boddy *et al.*, 1972)
σ = Standard error
TBK = Total body potassium
LBM = Lean body mass
SFT = Skinfold thickness
** = Estimated from total body potassium (Boddy *et al.*, 1972)
‡ = Estimated from skinfold thickness (Boddy *et al.*, 1974)

Table II

Clinical and Biochemical Status of the Patients

Patient No.	Treatment Shohl's mixture ml/day	Acid Base Status† (mEq/l)		Extracellular fluid volume (litres)	
		Plasma Bicarbonate	Plasma Chloride	Actual	Predicted
1	90	31 (25-30)	99 (97-104)	13·1	13·1
2	150	21 (18-29)	110 (103-112)	13·8L	17·4
3	150	22 (18-23)	105 (104-112)	15·4L	19·5
4	90	23 (18-26)	108 (103-113)	19·0H	14·0
5	90	26 (24-43)	104 (101-104)	16·3	16·9
6	120	28 (21-25)	104 (100-109)	17·0	17·7
7‡	90*			not estimated	
8§	120*	30 (24-27)	101 (99-102)	18·9	18·8
9	100	21 (19-25)	110 (107-110)	12·5	12·8
10	120	27 (19-26)	100 (107-110)	21·2	19·5
11F§	nil*	22 (19-26)	109 (96-105)	not estimated	

Key: F = female, * = also taking potassium supplements, ‡ = respiratory insufficiency and dehydration, § = congestive heart failure, † = current measurement with range over previous year in parentheses, H = high, L = low.

Total body potassium was measured in each patient, using a mobile shadow-shield whole-body monitor of high sensitivity (Boddy, 1967), by detection of γ-rays emitted by the naturally-occurring radioactive isotope ^{40}K, which is a constant proportion (0·0118%) of non-radioactive potassium. The counting-rate was expressed as mEq K using the calibration procedure described elsewhere (Boddy *et al.*, 1971). A blood sample was withdrawn from each patient on the day of monitoring and the plasma potassium, bicarbonate and chloride concentrations were estimated.

The measured total body potassium in each patient was compared with the predicted normal value and range for the individual, based on height, age and weight and also on height and age only (Boddy *et al.*, 1972) and lean body mass was calculated (Boddy *et al.*, 1972) from the measured total body potassium results.

The skinfold thickness was measured as described elsewhere at 2 sites, the subscapular and the triceps (Tanner, 1959). The measurements were used to estimate the fat content and, by difference, the lean body mass of each patient, using the appropriate equations of Durnin and Womersley (1974) and Siri (1956).

Extracellular fluid volume was measured using ^{51}Cr-E.D.T.A. (Garnett, Parsons and Veall, 1967).

Results

Relevant clinical data, the measured and predicted normal total body potassium values and the concurrently measured plasma potassium results are summarised in Table I. The acid-base status is shown in Table II.

The measured total body potassium was not significantly different from the "normal" value predicted from height and age in any of the patients ($P > 0·05$) and was only significantly different from that predicted from height, age *and* weight in case 3 ($P < 0·05$), who had a higher total body potassium than predicted. In the series as a whole, the measured values were not significantly different (paired t-test, $P > 0·10$) from the "normal" values predicted by either equation.

The normal range of plasma potassium for the reporting laboratory is 3·5 to 5·0 mEq/l. Only 2 patients had plasma potassium concentrations outwith this range at 5·3 and 5·9 mEq/l respectively.

The 3 patients with the lowest total body potassium compared with their expected normal (patients 3, 6 and 10) did have low normal plasma potassium concentrations (3·7 to 4·1 mEq/l). The patient with the highest total body potassium relative to his height, age and weight (no. 7) had the plasma potassium concentration of 5·3 mEq/l. Despite this there was no statistically significant correlation between plasma potassium and total body potassium. The 3 patients taking potassium supplements were indistinguishable from the rest.

Total body water was not measured in our patients but the extracellular fluid volume (ECFV) at the time of the whole body potassium measurement (Table II) was within ±1 standard deviation of the predicted ECFV value (Skrabal, Arnot and Joplin, 1973) in 6 of the 9 patients in whom it was measured. A paired t-test of the group showed that the measured ECFV was not significantly different ($P > 0·70$) from the predicted ECFV.

The measured skinfold thicknesses are summarised in Table I together with the lean body mass estimates derived from them and from the total body potassium determinations. The lean body estimates in the individual patients are in fair agreement and do not differ significantly (paired t-test $P > 0·05$). The values of measured total body potassium per kg lean body mass (from the skinfold measurements) are also given in Table I. The mean value for the male patients was 62·0 mEqK/kg LBM.

Discussion

To estimate the expected "normal" value of total body potassium, for comparison with the actual value measured by whole body monitoring, we used regression equations obtained previously

(Boddy *et al.*, 1972) of total body potassium on height, age and weight and also on height and age only. Although the coefficient of variation of total body potassium on height and age is marginally greater than when weight is included as an additional variable, there is a highly practical advantage that weight-related aberrations are obviated. In the whole series, there was no evidence of a significant potassium deficiency whichever of the two regression equations was applied. In our results, there was only a slight suggestion that plasma potassium could in some cases be a rough guide to total body potassium if the former was high or low, but there are too many other patients with normal plasma potassium values for this to be of much clinical importance.

The estimates of lean body mass (percentage body weight) in these patients, obtained from calculations of percentage fat content derived from skinfold thickness measurements, were compatible with those found previously in healthy controls (Boddy *et al.*, 1972). The mean value for the potassium content of lean body mass of 62·0 mEq/kg LBM was similar to that in the control males (Boddy *et al.*, 1974) and with the literature values reviewed elsewhere (Boddy *et al.*, 1973). Corresponding conclusions can be drawn for the single female patient. These data support the conclusion that the total body potassium in the present patients was not abnormal.

Ansell *et al.* (1961) reported a one-third deficit in "total body potassium" (exchangeable potassium measured by isotope dilution) in their patients with uretero-colic anastomoses. In their study the use of combined faecal and urinary excreta may have rendered isotope dilution inapplicable. Furthermore, the samples were obtained at 24 hours, rather than at 48 hours as generally recommended (Skrabal *et al.*, 1973).

Despite the clinical importance of possible changes in total body potassium following ureterosigmoid anastomosis (Stamey, 1956; Ansell *et al.*, 1961) and despite the unreliability of the plasma potassium concentration as an indicator of total body potassium, only one study has measured the total body potassium directly in this clinical condition (Williams *et al.*, 1967). This report was of concern because, like the work of Ansell *et al.* (1961), it revealed an apparent deficiency of potassium in the majority of patients with uretero-colic anastomoses, but not in a group of patients with ileal conduits. The expected normal total body potassium values in the study of Williams *et al.* (1967) were predicted from measurements of total body water in the patients and the use of regression equations of total body potassium on total body water obtained in a series of normal subjects. As there may be aberrations in body water in patients with ureterosigmoid anastomoses it is not known if data so derived from normal subjects is directly applicable to these patients. (ECFV was normal in the majority of patients described here, but the total body water content could have been abnormal.) The use of total body water measurements as a basis for the prediction of the expected total body potassium may lead to erroneous results, at least in some patients who, if under-treated, may have become either dehydrated, sodium depleted, or both (Desprez *et al.*, 1955). Dehydration, however, would lead to an under-estimate of the expected total body potassium when based on total body water estimations, and would tend to mask any deficiency. Although the patients of Williams and his colleagues were active and ambulant and not in an "acute episode of imbalance", concurrent treatment, in particular with alkali, was not mentioned. It is not certain, therefore, that hyperchloraemic acidosis had been completely and persistently abolished in their patients over an appreciable period of time prior to measuring their body potassium. If undertreated, minimal or even moderate acidosis may have been present, despite the absence of symptoms, and such acidosis could have led to depletion of body potassium content. This explanation is inevitably somewhat speculative and, in view of the clinical importance of body potassium further investigation seems warranted. All but the most recently acquired of our patients were receiving oral supplements of sodium citrate in amounts demonstrably sufficient to prevent the emergence of either systemic acidosis or hyperchloraemia.

The association between acidosis and potassium depletion has been remarked on by Janknegt (1967). The possible causal associations between acidoses and potassium loss are somewhat paradoxical since it is metabolic alkalosis which is customarily associated with increased urinary potassium excretion. However, extra-cellular acidosis causes a withdrawal of potassium from intra-cellular into extra-cellular fluid (Swan and Pitts, 1955) where, in patients with uretero-sigmoid anastomoses, it would be more easily lost together with sodium during the osmotic diuresis associated with increased blood urea concentrations (Anslow and Wesson, 1955).

Conclusions

Our findings of normal levels of total body potassium clearly conflict with the deficiency of potassium in patients with colonic urinary diversion reported by Ansell *et al.* (1961) measuring exchangeable potassium and by Williams *et al.* (1967) measuring total body potassium. It may well be that the development of potassium depletion in uretero-sigmoid anastomotic states is determined by the tendency to systemic acidosis. When acidosis is remedied and kept in abeyance potassium depletion may be obviated. This report shows that potassium depletion is not inevitable in patients with uretero-sigmoid anastomoses.

Summary

Total body potassium was measured by whole body counting in 11 patients with uretero-sigmoid anastomoses who had undergone cystectomy 4 months to 13 years previously.

The measured total body potassium was not significantly different in any of the patients from the "normal" value for the individual patients, predicted from height and age. It was only significantly different from that predicted from height, age *and* weight in 1 patient.

In the series as a whole, the measured values of whole body potassium were not significantly different from the "normal" values estimated by either relationship.

From measurements of skinfold thickness, the lean body mass of each patient was estimated. The mean potassium content, 62·0 mEq/kg LBM in the male patients was within the normal range.

The absence of potassium depletion may derive from the successful abolition of hyperchloraemic acidosis by long-term alkali therapy.

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Oestrogen Therapy and Serum Cortisol in Carcinoma of the Prostate

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Exogenous oestrogens and pregnancy induce adrenocortical hyperactivity as evidenced by the elevation of serum cortisol levels observed in these situations. The fact that there is a concomitant increase in the amount of corticosteroid-binding globulin (CBG), has led to the postulation that the hyperactivity of the adrenal cortex in these cases lacks clinical significance (Daughaday and Mariz, 1961; Slaunwhite *et al.*, 1962).

Glucocorticoids cause, among other effects, an involution of lymphoid tissue. An evaluation of serum cortisol and the circulating lymphocyte population in cancer patients receiving exogenous oestrogens may possess clinical significance due to the positive and significant correlation between cancer prognosis and peripheral lymphocyte counts reported in several studies (Riesco, 1970; Swank *et al.*, 1971).

Patient Population and Methods

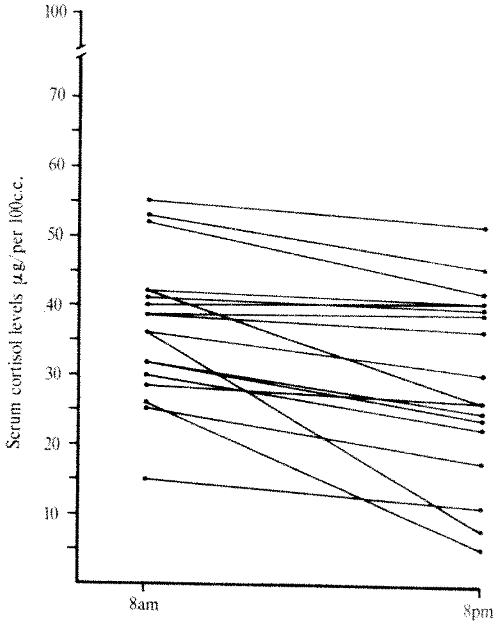
Twenty patients with histologically documented carcinoma of the prostate gland, previously castrated and who were on oestrogen therapy for at least 6 months, were investigated. In every case peripheral blood samples were obtained at 8 a.m. and 8 p.m. for serum cortisol determination by the method of competitive binding analysis (Murphy, 1967). Total and differential white cell counts (WBC) were carried out on peripheral blood samples. The same investigations were performed on 20 patients with carcinoma of the prostate, prior to institution of hormonal treatment. A close age matching of treated patients and controls was not carried out; the former group averaged 66·9 years of age and the controls 60·8 years.

Results

The levels of serum cortisol in patients with a prostatic neoplasm and receiving oestrogen therapy are depicted in Figure 1, while comparable data for the control patients appears in Figure 2. The average morning value for the oestrogen treated patients was 40·7 μg/100 cc, compared to 21·8 μg/100 cc for controls. The difference between these 2 distributions was statistically significant ($P<0{\cdot}001$ with the Mann-Whitney test). Furthermore, the decline in serum cortisol levels at the end of the day was markedly less in the treated patients than in the control, with an average decline of only 21·7% in the former versus 57·8% in the latter. This data is also significant ($P<0{\cdot}001$ with the Chi-square test).

The determination of circulating lymphocytes in peripheral blood showed an average count of 11·6% of WBC for the oestrogen treated group, versus an average of 20·1% of WBC for the controls. There is a significant difference between these 2 distributions ($P<0{\cdot}001$, Mann-Whitney test).

The finding of both elevated serum cortisol and a decrease in the number of circulating lymphocytes in the oestrogen treated patients suggests the possibility of an inverse relationship between



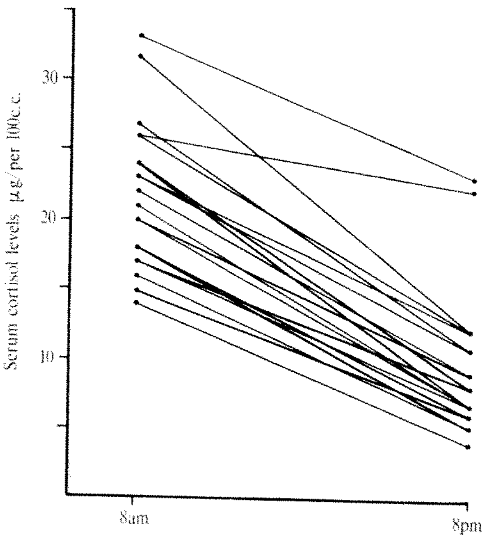


Fig. 1. Determination of serum cortisol in the cancer group. With 2 exceptions, the serum levels are maintained throughout the day.

Fig. 2. Serum cortisol levels in the control group. Diurnal variation is well maintained. Note different scale from Figure 1.

these 2 variables. The significance of this finding was evaluated by calculation of the correlation coefficient in individuals within the oestrogen group and the untreated group, separately. A correlation coefficient between these 2 variables of −0·49 was found in the cancer group, which is statistically significantly greater than 0 at the 0·05 level of significance. The correlation coefficient was only −0·24 in the control group, which is not significant.

Discussion

More than 50 biological alterations have been associated with oestrogen therapy (Lancet, 1969), but we are not aware of a previously reported relationship between oestrogen administration and lymphopenia. This study cannot establish positively the cause of lymphopenia in the group of oestrogen treated cancer patients, in whom the disease was, obviously, more advanced than in the control group. Previous castration or an undetermined tumour factor may have played a role in its development. It will be of interest to investigate patients receiving exogenous oestrogens for reasons other than an oncolytic effect, *e.g.*, contraception.

The effects of various hormones on the immune system have been extensively studied (Kaye and Jones, 1971; Claman, 1972). Oestrogens in particular are reported to produce a significant increase in phagocytic activity (Nicol, Vernon-Roberts and Quantock, 1965; Magarey and Baum, 1971). Moreover, castration in the experimental animal produces marked changes in humoral immune reactivity which may be enhanced further by the addition of adrenalectomy (Eidinger and Garrett, 1972). Equally extensive is the evidence pointing to significant alterations in cell-mediated immunity following oestrogen administration; several *in vitro* studies have shown a depressed lymphocyte response to mitogens in humans receiving exogenous oestrogens (Hagen and Froland, 1972; Fitzgerald, Pickering and Fergusson, 1973; Pentycross *et al.*, 1973). A similar situation has been found in pregnant women (Purtillo, Hallgren and Yunis, 1972). Thus, there is considerable evidence indicating remarkable changes in immune reactivity induced by oestrogens. Whether these effects are direct or not, remains to be determined.

It can be theorised that the influence of oestrogen therapy on the lymphoreticular system is indirect and probably mediated through the adrenal cortex in 2 different ways. It is generally accepted that the total plasma cortisol level, in humans, is increased following the administration of oestrogens. However, it is less certain whether free biologically active cortisol is also increased (Bulbrook *et al.*, 1973). Mills *et al.* (1960) found no changes in the levels of non-protein-bound cortisol after treatment with oestrogenic compounds. On the contrary, Doe *et al.* (1960), Murray (1967) and Burke (1969) have reported a significant increase in the values of free cortisol in the serum of oestrogen treated patients. Glucocorticoids produce a marked depression of the lymphoreticular system (Gabrielsen and Good, 1967; Claman, 1972). Conversely lymphoid hyperplasia and lymphocytosis have been reported following adrenocortical inhibition (Morales, Jalali and Garvie, 1972) and adrenalectomy (Holt and Lee, 1971). It appears, then, that oestrogen induced adrenal hyperactivity may be an additional factor in the development of lymphopenia in these patients.

Hyperplasia of the adrenal is known to occur both after oestrogen therapy and after orchidectomy (Fergusson, 1972). Since the patients studied here were treated by the two modalities it is impossible to attribute exclusive responsibility for the recorded changes to either one of them.

Finally another effect of oestrogens, mediated through the adrenal cortex and affecting mechanisms of immune recognition and response should be mentioned. Apffel and Peters (1969) and others (Cooperband *et al.*, 1972) have postulated an impairment of immune surveillance by an α-2-globulin in patients with prostatic cancer receiving oestrogens. Interestingly enough, the levels of α-globulin increase during pregnancy and exogenous oestrogen administration (Cooperband *et al.*, 1968; Musa, Seal and Doe, 1965). The correlation between these 2 clinical situations, serum protein levels and immune reactivity is at present under study.

Summary

Patients with prostatic cancer, receiving oestrogen therapy were found to have elevated serum cortisol levels and lymphopenia. Oestrogens are known to have a profound effect on the immune system; the possibility that this effect is mediated through the adrenal cortex is discussed. The significance of these findings, however, remains to be determined.

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Serial Fluorine-18 Bone Scans in the Follow-up of Carcinoma of the Prostate

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Carcinoma of the prostate has the highest incidence of all urogenital neoplasms in the male, being responsible for 4,027 deaths in the United Kingdom in 1971 (Registrar General). The majority of cases of carcinoma of the prostate are first diagnosed when the disease is advanced; early diagnosis is uncommon, except in those cases discovered on microscopic examination of either the resected or enucleated specimen in patients with benign hyperplasia.

Even when the diagnosis has been established there remain two unresolved problems in the management of these patients: (1) is the tumour confined to the prostate? and (2) how can either the progression of the disease or the response to treatment be determined?

Clinical staging has helped to advance our knowledge of the natural history of the disease and to assist in the management of patients, but it is now known that the information obtained from a radiological skeletal survey and measurement of the serum acid phosphatase, the minimum requirements for staging, is both inadequate and unreliable. Greater accuracy in the detection of osseous metastases has been claimed by the addition of bone biopsy (Nelson, Boatman and Flocks, 1973), bone marrow acid phosphatase determination (Chua *et al.*, 1970), and radio-isotope bone scanning (Kontturi and Kiviniitty, 1971, Roy *et al.*, 1971, Shearer *et al.*, 1974).

In this study we have examined the value of the bone scan, using cyclotron-produced fluorine-18 (^{18}F), for staging the disease and as a means of measuring the progression of the disease over periods of up to 5 years. The relationship between these scan data and treatment with oestrogens has been examined.

Patients and Methods

74 patients with carcinoma of the prostate were studied. Their ages ranged from 51 to 82 years (mean 71·5 years). 41 patients are alive and their mean age is 70·2 years and the mean duration of follow-up is 2 years and 10 months. The mean age of the patients who have died was 72·8 years and the mean survival following diagnosis was 3 years and 6 months.

In 65 patients the diagnosis was confirmed by histological examination of tissue obtained by either transurethral resection or from the enucleated specimen. The diagnosis was made by biopsy of a penile lump (1 case), an inguinal lymph node (1 case) and bone biopsy (1 case). In the remaining 6 patients the clinical diagnosis was supported by radiological evidence of metastases and raised serum acid phosphatase levels.

All patients were seen in a special clinic at either 3-monthly or 6-monthly intervals. A combined radiological and ^{18}F scan survey, chest X-ray and intravenous urogram was carried out at the time of diagnosis. The radiological and scan surveys were repeated annually and these were examined together by two of the authors (M. V. M. and J. P. L.).

Until 1970, the bone scans were performed 1 hour after a 2 millicurie dose of ^{18}F using 17 fields of the Nuclear Chicago Pho Gamma II scintillation camera and collecting 15 to 20,000 counts per field. In 1971 and the first half of 1972 rectilinear scans were performed 1 hour after 2 millicuries of ^{18}F with the scanner set to collect 360 counts per cm^2 from normal areas of spine. Subsequently, scans have been performed 2 hours after a dose of between 5 to 10 millicuries of ^{18}F, with the rectilinear scanner set to collect 1,200 counts per cm^2 from normal spine (Merrick 1973).

Clinical Staging

The tumours were staged according to the system used by the Veterans Administration Co-operative Urological Research Group (VACURG) as follows:

Stage 1 (or A). Tumour confined to the prostate and not palpable. Carcinoma incidentally diagnosed on pathological examination of the prostate. Normal serum acid phosphatase. No skeletal metastases.

Stage 2 (or B). Tumour confined to the prostate but palpable on rectal examination as a "nodule". Normal serum acid phosphatase. No skeletal metastases.

Stage 3 (or C). Locally invasive tumour with diffuse involvement of the gland. Normal serum acid phosphatase. No skeletal metastases.

Stage 4 (or D). Distant metastases. The prostate may vary from either normal (*i.e.* occult tumour) to obvious periprostatic spread.

20 patients in this study underwent prostatectomy for what was considered to be benign prostatic hypertrophy but histological examination revealed a focus of carcinoma in the adenoma (*i.e.* Stage 1). In 4 of these patients the initial bone scan showed an abnormal uptake of isotope consistent with metastases while the X-rays were normal and the serum acid phosphatase values were not elevated, so that these 4 patients were restaged as having Stage 4 disease. A prostatic "nodule" was an incidental finding in 5 patients who had no urological symptoms—(Stage 2). Thus, 53 patients (71·6%) were first diagnosed when the disease was advanced; either Stage 3 or 4 (Table I).

Table I

Clinical Staging of Patients with Carcinoma of the Prostate

Stage	No. of Patients	%
1	16	21·6
2	5	6·8
3	11	14·8
4	42	56·8
Total	74	100

Table II

Initial Treatment following Diagnosis of Carcinoma of the Prostate

	Stage				
Treatment	1	2	3	4	No. of patients
Stilboestrol	11	4	5	36	56
Orchidectomy	2	0	2	3	7
No treatment	3	1	4	3	11
Total	...	...	...	...	74

Treatment

63 patients were treated with stilboestrol and/or castration from the time of diagnosis. Stilboestrol was commenced in a dose of 90 mg daily until the effects of the drug were evident by breast enlargement and clinical improvement. This was followed by a regular maintenance dose of 15 mg daily. Initially, all patients were treated with this regime unless contra-indicated. However, over the past 2 years the dose of stilboestrol has been reduced to 3 mg daily and only patients with Stage 3 and 4 disease have been treated, while asymptomatic patients with early localised disease have not been treated.

7 patients with co-incident cardiovascular disease were considered unsuitable for oestrogen therapy and these patients underwent orchidectomy as a primary method of control. 11 patients did not receive any form of treatment; of these, 4 were Stage 1 or 2. While in 7 patients with advanced disease treatment was either delayed or death occurred before treatment was commenced (Table II). Hypophysectomy (by transnasal yttrium-90 implant) was carried out in 3 patients with widespread painful bone metastases.

Of the 56 patients treated with stilboestrol 27 are alive and the mean duration of follow-up is 2 years and 9 months. 29 patients have died and the mean survival in this group was 2 years and 4 months. It was necessary to discontinue stilboestrol in 27 patients owing to the development of cardiovascular complications or intolerable side effects and 22 of these underwent orchidectomy. Within 3 months to 2 years of the commencement of treatment with oestrogens 19 patients (32%) developed cardiovascular complications and in 5 patients these complications were the direct cause of death (Table III).

Results

140 scans with their corresponding X-rays were available for study (Table IV). The large number of patients with a single scan is due to the inclusion of patients at the beginning of the study who had advanced disease and were being followed-up. 40 patients have been followed for 2 years and 8 of these for 4 years.

Table III

Incidence of Vascular and Cardiac Complications in 56 Patients treated with Stilboestrol

Complication	No. of patients
Congestive cardiac failure	10
Deep venous thrombosis	4
Myocardial infarction	3
Cerebrovascular accident	2
Total	19

Table IV

Number of Patients with Carcinoma of the Prostate followed with Annual 18-Fluorine Bone Scans and Skeletal Surveys

Follow-up	Patients	Alive	Dead
4 years	8	6	2
3 years	10	6	4
2 years	22	12	10
1 year	34	17	17
Total	74	41	33

Table V

Correlation of Scan with X-ray Results in 74 Patients. Of the 44 Patients with no Radiological Evidence of Metastases, 11 (25%) had an Abnormal Bone Scan

	X-rays	
	Metastases	No metastases
	30	44
Scan −	0	33
Scan +	30	11
	100% Scan +ve X-ray +ve	25% Scan +ve X-ray −ve

30 patients had radiological evidence of metastases and all of these had a positive bone scan. 44 patients had no evidence of metastatic disease on conventional radiography, however, in 11 of these (25%) the initial ^{18}F bone scan was positive. There were no false negative bone scans (Table V). In 17 patients the scan showed abnormal uptake of isotope which was due to non-malignant lesions (osteo-arthritis in 13 and Paget's bone disease in 4). The areas of increased uptake corresponded to lesions on X-ray and the diagnosis was confirmed by biopsy or at autopsy.

Of the 11 patients who had a positive scan and negative X-rays, 5 are alive and 6 have died. In 4 of the patients who died metastases became evident on X-ray within 2 years and were confirmed at post-mortem (Fig. 1). In 2 patients the scan was positive but X-rays up to the time of death showed no evidence of metastases. Only 1 of these patients came to autopsy, where extensive skeletal metastases corresponding to the areas of increased uptake of isotope were confirmed. Of the 5 patients who are alive, 1 patient remains X-ray negative at 2 years, while 1 patient has developed radiological appearances consistent with metastatic deposits at 3½ years after the initial positive bone scan. A bone biopsy of the suspicious area confirmed the presence of tumour. The remaining 3 patients have had only one set of scans and X-rays.

Of the 30 patients in whom the X-rays and scans were positive for metastases 13 are alive and 17 have died. 6 of the 13 live patients have had 2 scans. 3 patients have been followed for 4 years; one of these has shown complete resolution of bone lesions on treatment with oestrogens and the bone scan and X-ray are now normal. In the second patient the scan and X-ray appearances remain unchanged and in the third patient clinical deterioration was accompanied by extension of the skeletal abnormalities. 4 patients are newly diagnosed and have only had one set of investigations.

Of the 33 patients with no radiological or scan evidence of metastases 22 are alive and 11 have died. Only 1 of these patients has become scan positive, but remains X-ray negative (Fig. 2). 13 of the 33 patients have been followed for 3 or more years and these patients show no evidence of skeletal metastases. 1 patient has become scan and X-ray positive within 6 months. In the remaining 7 patients only one scan has been performed. Autopsies were carried out in 6 of the 11 patients who died; in 5 of these there was no evidence of skeletal metastases, but in 1 patient extensive soft tissue tumour deposits were present but there was no evidence of bone involvement.

Discussion

The detection of skeletal metastases by X-rays depends upon the destruction of 50 to 70% of the invaded bone (Edelstyn, Gillespie and Grebbell, 1967). It is now well recognised that scanning with bone-seeking radioisotopes is superior to conventional radiology in the detection of early metastatic lesions (Williams, Blahd and Wetteraa, 1968; Kontturi and Kiviniitty, 1971; Shearer *et al.*, 1974). The value of fluorine-18 as a bone scanning agent was first reported by Blau, Nagler and Bender (1962). This study has shown that fluorine-18 is a useful radiopharmaceutical agent for bone scanning in malignant disease of the prostate. Reports on the use of other radio-isotopes, (strontium-85, strontium-87m and technetium complexes) have continued to show that metastases

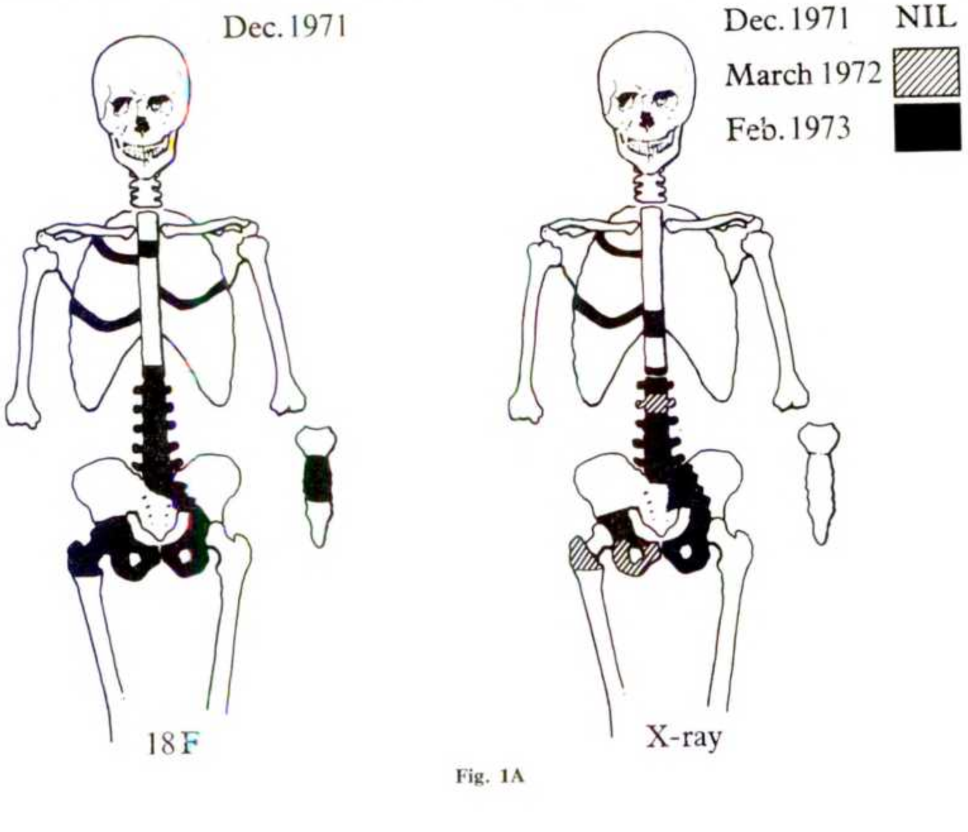

Fig. 1A

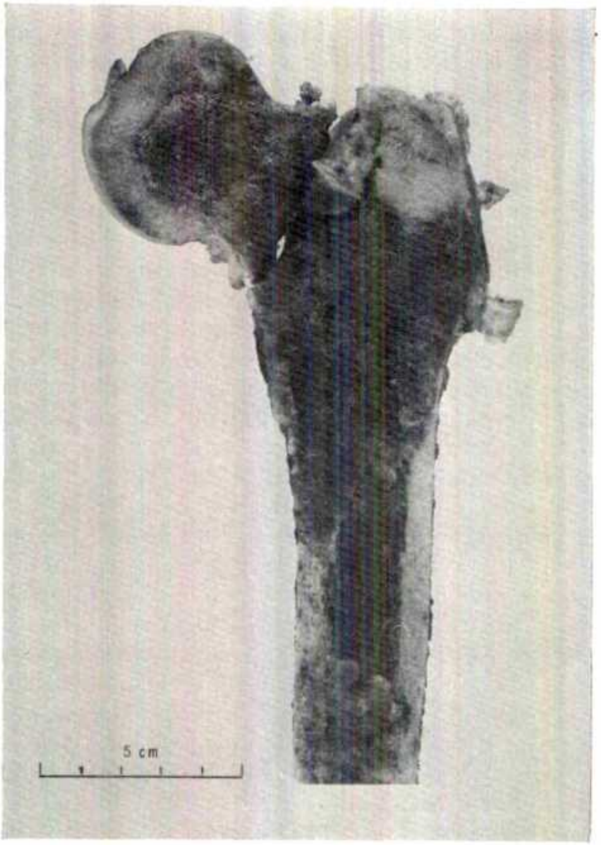

Fig. 1B

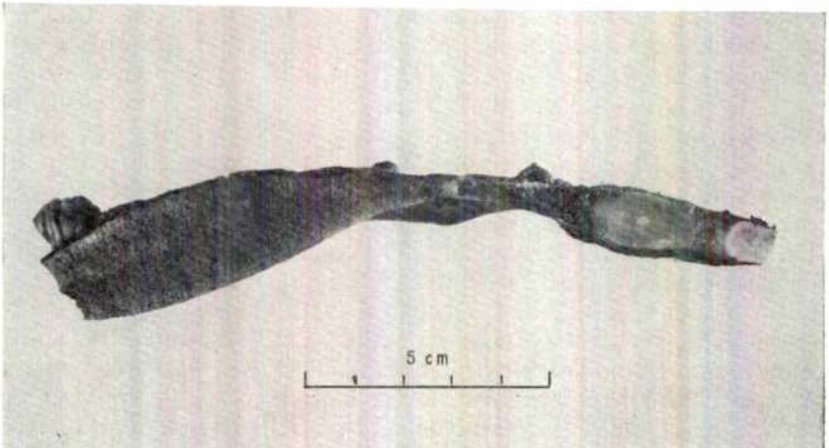

Fig. 1C

Fig. 1. A, Case 1 (F. C.). Radiological survey in December 1971 was normal, 18-F bone scan showed abnormal uptake of isotope in the shaded area. X-ray in March 1972 showed secondary deposits in the hatched area. X-ray in February 1973 showed widespread deposits but the scan abnormalities were more extensive than those seen on X-ray. B, Macroscopic osits in scan-positive areas—right femur. C, Macroscopic deposits in scan-positive areas—vertebrae.

not visible on X-rays can be detected by scanning methods—an important consideration in the staging and management of patients. In this study scanning helped to establish the correct stage of the disease in 25% of patients which included 4 patients with an incidentally diagnosed carcinoma, who would have been considered to be Stage 1 were it not for the presence of an abnormal bone scan.

The incidence of abnormal scans where no lesion can be seen on the corresponding X-rays has varied from 17% using strontium-85 (Johnson and Haynie, 1972) to 52·6%, using fluorine-18 (Roy *et al.*, 1971). The high value in the latter report is now recognised to be due to a biased group of patients available at the beginning of the study and to the scanning methods and their interpretation. The incidence of abnormal scans in the presence of normal X-rays in this report is 25%. False negative scans have not been reported with fluorine-18 but false negative scans have been reported with strontium 85 and strontium-87m (Johnson and Haynie, 1972; Shearer *et al.*, 1974). We have continued to see a number of patients (23%) in whom non-malignant lesions, *i.e.* Paget's disease and osteo-arthritis, resulted in an abnormal scan. It is, therefore, necessary to examine the scans with corresponding X-rays to enable correct interpretation of the scan since the distinction between metastatic lesions and other forms of bone disease is not apparent on the scan alone. In doubtful cases a bone biopsy should be performed to confirm the diagnosis.

In the present study the scan and X-ray appearances were followed in some patients for up to 5 years. Of the 11 patients with positive scans but negative X-rays; 5 developed radiological lesions within 2 years and in 1 case the X-rays became positive 3½ years after the initial (positive) scan. Metastatic tumour deposits were confirmed by bone biopsy at autopsy. Johnson and Haynie (1972) followed a group of patients for periods of 4 to 17 months without metastatic disease developing on X-ray. In a study of carcinoma of the breast scan abnormalities preceded radiological confirmation by 2 to 18 months (Galasko, 1972). It is now evident from our study that the change from X-ray negative, scan positive to X-ray positive over an extended period indicates progress of the disease rather than healing bone lesions.

Every case with radiological abnormalities had an abnormal scan. In many instances the bone scan showed more extensive involvement than the X-rays. In following the progress of this group of patients with hormone therapy a favourable response to treatment was indicated by clinical improvement, relief of bone pain and radiological evidence of healing or regression of bone lesions. However, the fluorine-18 bone scan remained unchanged but this is not surprising since the uptake of isotope reflects osteoid response. Only 1 patient became scan and X-ray negative on oestrogen therapy. It has been suggested that a failure to change from scan positive to scan negative implies a hormone resistant tumour (Shearer *et al.*, 1974); this has not been evident in the present study where we have seen clinical and radiological improvement but the scan remains unchanged.

The majority of patients with a normal scan have remained so and only 2 patients in whom the fluorine-18 scan was initially normal has developed a scan abnormality during the period of follow-up; however, it is expected that more patients in this group will develop abnormalities as they are followed for longer periods.

All of the patients in this study were managed by conservative methods (Chisholm, 1974). The proportion of incidentally diagnosed carcinoma (21·6%) was generally higher than in other reported series (Varkarakis, Castro and Azzopardi, 1970); it has been suggested that if these patients have a life expectancy of 10 years or more, then a radical prostatectomy is the treatment of choice (Lehman *et al.*, 1968, Veenema, Lattimer and Gursel, 1973). However, none of our patients would have fulfilled the criteria for radical prostatectomy and we would agree with Meares (1972) that patients with a Stage 1 lesion should not be treated with either operation or oestrogens.

Most of our patients were treated initially with stilboestrol but in 27 patients (50%) treatment had to be discontinued and the majority underwent orchidectomy. 32% of patients developed cardiovascular complications within 2 years of commencing treatment. There is now substantial evidence that oestrogens carry a high risk of cardiovascular complications, that the major hazard occurs in the first year and that a history of cardiovascular disease is a predisposing factor

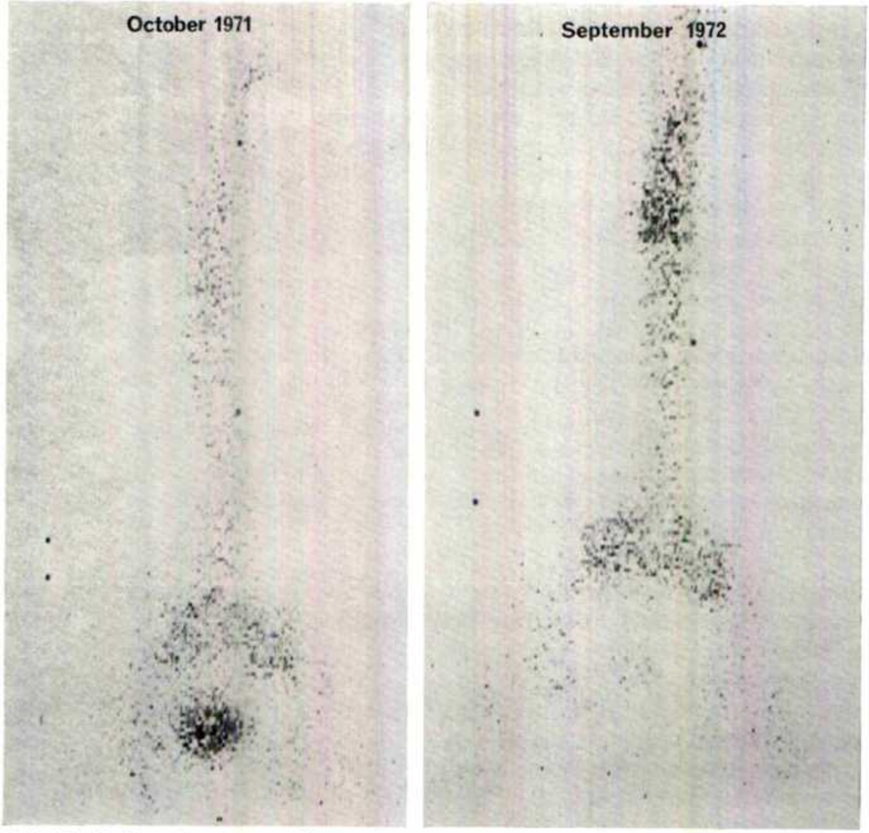

Fig. 2. Case 2 (R. B.). Incidental carcinoma diagnosed at prostatectomy in 1970. Initial gamma camera scan and X-rays were normal. Stilboestrol commenced but discontinued 1 year later following a cardiovascular accident. Patient refused orchidectomy. 18-F scan in 1971 was normal but the scan in 1972 showed abnormal uptake of isotope in the dorsal vertebrae and the pelvis while the skeletal survey, which showed osteoarthritis, remained unchanged.

(Blackard *et al.*, 1970). Initially our patients were given large doses of stilboestrol as there was some evidence that this achieved better control (Fergusson, 1963). It has now been demonstrated that a smaller dose of oestrogen (1 mg daily) is effective in suppressing androgen production (Bailar and Byar, 1970; Robinson and Thomas, 1971). Within the last 2 years of this study we have reduced the dose of stilboestrol to 3 mg daily for all patients with advanced disease. Whether or not a higher dose is more effective in tumour control by its direct action remains uncertain but what is certain is that the lower dose has been associated with fewer cardiovascular complications.

Summary

74 patients with prostatic cancer were studied annually by combined radiological and fluorine-18 scan survey over a 5-year period.

The results of the long term follow-up of bone scans is reported.

At the time of the initial diagnosis 71·5% of the patients had advanced disease and 56% had radiological or scan evidence of metastases. A critical evaluation of the scans resulted in the detection of early bone lesions in 25% of patients with no radiological evidence of metastases. Follow-up of these patients has shown that scan abnormalities preceded radiological changes from between 1 to 4 years and there was good correlation proven histologically by bone biopsy or autopsy in more than half of the patients. In patients with a positive bone scan and positive

X-rays the scan abnormalities were more extensive than the corresponding X-ray lesions. When bone healing occurred with endocrine treatment this was more readily apparent on the X-rays. False negative scans were not seen with fluorine-18 which allows for greater accuracy in the detection of skeletal metastases.

Bone scanning has enabled correct staging to be carried out.

This study confirms the high incidence of cardiac and vascular complications in patients treated with oestrogens.

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Plasma Zinc Levels in Prostatic Disease

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Many papers have appeared in the literature regarding the high tissue concentration of zinc in the normal prostate; this concentration is known to decrease with oestrogen therapy (Hoare, Delory and Penner, 1956) and in prostatic cancer (Mawson and Fischer, 1952; Hoare, Delory and Penner, 1956; Schrodt, Hall and Whitmore, 1964) but to be greatly increased in prostates of patients with benign hyperplasia (Schrodt, Hall and Whitmore, 1964). However, no detailed study has yet appeared in the literature regarding plasma zinc concentrations in these conditions and whether it may be considered to be a useful biochemical test for the diagnosis of prostatic disease or be a meaningful monitor during the ensuing period. In this study plasma zinc concentrations have been estimated in patients with benign prostatic hyperplasia and prostatic adenocarcinoma, and compared with age and sex-matched controls. The results have been assessed to see if there was any correlation between these diseases of the prostate and plasma zinc concentrations.

Patients and Methods

14 patients with benign hyperplasia and 64 patients with prostatic carcinoma were studied. 63 normal men and 54 normal women were also studied in order to obtain control values; their ages ranged from 20 to 80 years. The prostate in a male over 50 years was considered to be normal provided that he had no urinary symptoms and that the prostate on rectal examination was normal.

Blood samples were taken for plasma zinc estimation between 9 a.m. and 11 a.m. to exclude any possible diurnal variation. None of the normal subjects or patients was fasting. They did not have a rectal examination or indwelling catheter for several days before the blood was taken, to exclude the possibility of prostatic manipulation influencing the result.

The blood was anticoagulated with heparin and centrifuged as soon as it reached the laboratory. Red cells have a high zinc content, and haemodialysis will increase the plasma levels (Rose and Willden, 1972) and hence any haemolysed specimens were rejected. The same plasma sample was used for the following estimations:

(1) Plasma zinc, by the deproteinisation method of Parker, Humaller and Mahler (1967) using a Perkin-Elmer 290 B atomic absorption spectrophotometer.
(2) Plasma alkaline phosphatase, using the method of Bessey, Lowry and Brock (1964).
(3) Total and "tartrate-labile" acid phosphatase using the colorimetric 4 amino-antipyrene method of King and Jegatheesan (1959).
(4) Plasma urea and creatinine using standard Technicon Auto-Analyser techniques.

A record was kept of any hormonal therapy a patient had received. Patients with plasma creatinine levels above 2 mg/100 ml were excluded since an alteration in renal function will change the plasma zinc concentrations (Rose and Willden, 1972).

Results

Since all of the patients with either hyperplasia or malignancy were over 55 years of age, the control values for plasma zinc concentration were divided into over 55 and under 55 in order to provide a basis for comparison. In the males, a statistically significant rise was found in the 55+ age-group ($P < 0{\cdot}05$, Student's *t*-test); in contrast, in the females there was a significant fall in the plasma zinc concentration with age ($P < 0{\cdot}01$) (Fig. 1).

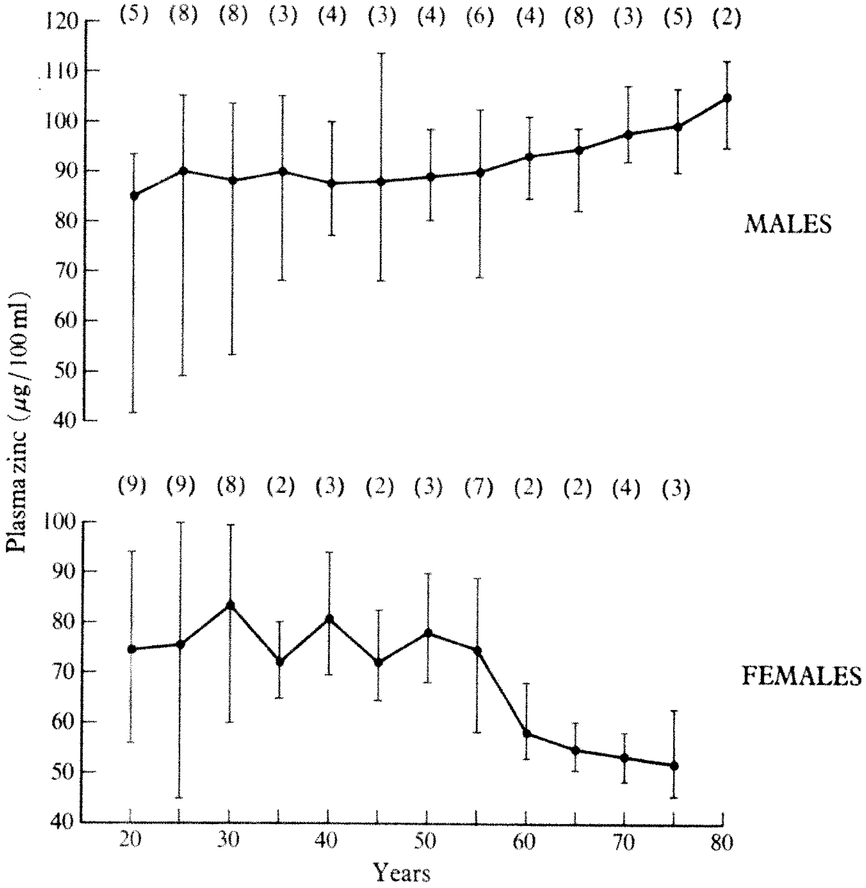

Fig. 1. Plasma zinc levels of normal adults with increasing age.

14 patients, who subsequently had retropubic prostatectomies for benign hyperplasia, had plasma zinc levels in excess of the normal range for their age-group (Table I). This difference is statistically significant ($P \leqslant 0{\cdot}01$)when compared with normals of the same age-group. There was not, however, any correlation between plasma zinc and the weight of prostatic tissue enucleated.

The patients with adenocarcinoma of the prostate were grouped into those without metastasis (24 patients) and those with metastasis (40 patients). There was no significant difference in plasma zinc levels between these two groups of cancer cases and the results for normal males in the prostatic carcinoma age-group (Table II, Fig. 2). Both groups of patients with carcinoma gave a wide range of results which are not diagnostic. In the group with metastasis it would appear from inspection of Table III that the mean plasma zinc level fell as the symptoms became more severe, but this may be misleading as it cannot be borne out statistically because of the small numbers involved.

There is no correlation between plasma acid or alkaline phosphatase levels and plasma zinc concentrations, although the phosphatase levels, as expected, increased with the advancement of the metastatic disease whilst zinc levels tended to decrease with the severity of the disease.

Discussion

It is known that in the normal male, the size of the prostate gland increases during the first 20 years of life, stabilises for a further period of 25 years and then generally undergoes a second period of growth.

Table I

Plasma Zinc Levels of Patients with Benign Hyperplasia

	Plasma Zinc μg/100 ml	
Normal males of the same age-group (28)	range	86-117
	mean	98·1
	S.D.	8·24
Benign hyperplasia (14)	range	94-186
	mean	153·8
	S.D.	15·5

( ) = Number of persons in each group.

Table II

Plasma Zinc, Acid-Phosphatase and Alkaline Phosphatase in Normal Men and Patients with Carcinoma of the Prostate

	Plasma Zinc μg/100 ml		Plasma Alkaline Phosphatase K.A. units/100 ml		Plasma Prostatic Acid-Phosphatase K.A. units/100 ml	
Normal males of same age-group (28) (55 years onwards)	range	86-112	range	4-13	range	0-0·8
	mean	100·0	mean	8·1	mean	0·36
	S.D.	8·24	S.D.	2·35	S.D.	0·21
Carcinoma of prostate with metastasis (40) (55 years onwards)	range	90-137	range	3·3-36·0	range	0·3-15·0
	mean	112·9	mean	18·0	mean	2·9
	S.D.	18·1	S.D.	10·5	S.D.	4·16
Carcinoma of prostate without metastasis (24) (55 years onwards)	range	90-143	range	4·4-11·1	range	0·2-2·0
	mean	113·7	mean	7·5	mean	0·83
	S.D.	21·3	S.D.	2·2	S.D.	0·47

( ) = number of persons in each group.

The prostate, seminal vesicles and testes have the highest concentrations of zinc in the body (Balogh and Szendroi, 1965). The concentration is lower in prostatitis and cancer (Daniel *et al.*, 1956; Voigt, 1958). In benign prostatic hyperplasia the zinc content of the gland is the same as that in normal prostate or even higher (Gallagher *et al.*, 1963; Schrodt *et al.*, 1964). Androgens increase the amount of zinc in prostatic tissue whereas oestrogens tend to reduce the number of samples with high prostatic zinc concentrations (Hoare *et al.*, 1956).

The increase in plasma zinc that was seen in the 55+ age-group may be explained in terms of increasing size of the prostate with age. This may also explain the trend in the plasma zinc levels in the "normal" group. The elevated levels in those patients with clinically diagnosed benign hyperplasia appears to be a useful index of that disease. The plasma zinc gave no indication of the size of the gland although it is possible that there might be some correlation if there were reliable methods for measuring the size of the prostate.

Plasma zinc estimations do not help in the diagnosis or clinical estimation of the degree of severity of carcinoma of the prostate. However, a diagnosis of malignant carcinoma of the prostate can be excluded in the case of a patient with a clinically assessed enlarged prostate gland

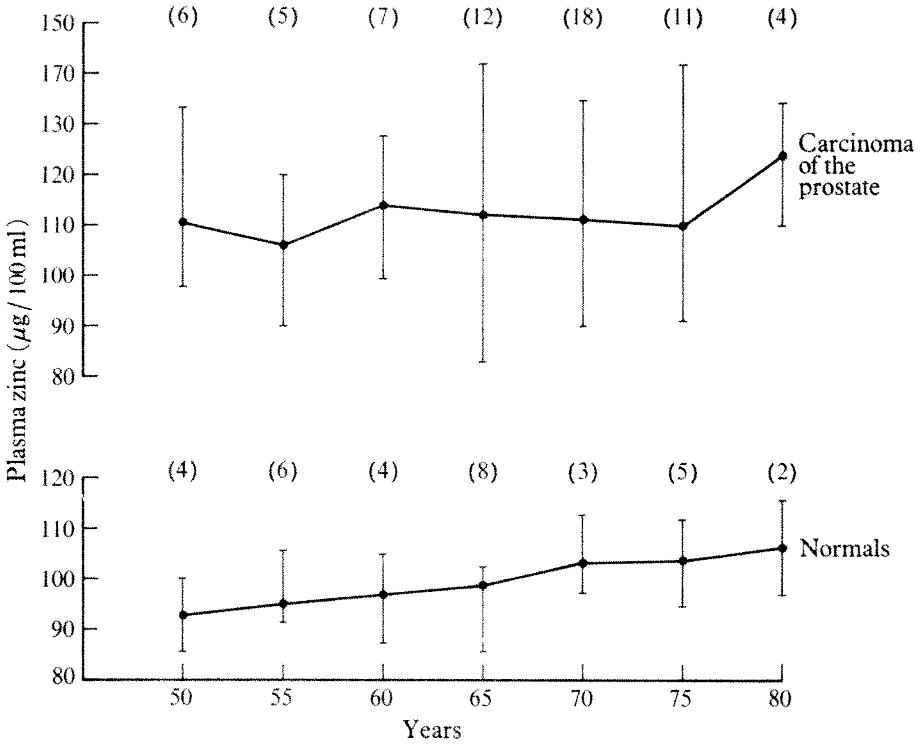

Fig. 2. Plasma zinc concentrations for normal and prostatic carcinoma patients.

Table III

Plasma Zinc and Alkaline Phosphatase in Prostatic Carcinoma with Metastases

Clinically Assessed (Symptoms untreated)	Plasma Zinc μg/100 ml		Alkaline Phosphatase K.A. units/100 ml	
	Mean	S.D.	Mean	S.D.
1. Mild (20)	114	10·1	25·6	5·46
2. Moderate (15)	105·2	12·1	20·6	19·15
3. Severe (5)	101·4	15·8	22·5	10·83

( ) = Number of persons in each group.

and a plasma zinc level over 120 μg/100 ml. The fall in plasma zinc concentrations seen in individual patients with increasing symptoms from metastases is probably a reflection of increasing debility rather than the amount of neoplastic tissue present.

The fall in plasma zinc concentrations seen in normal females following the menopause can tentatively be considered to be due to the change in hormonal environment following this event. It is known that the concentration of zinc in the prostatic *tissue* is decreased with oestrogen treatment but there were no changes in the *plasma* levels in the patients with carcinoma in this study. These observations support the view that zinc metabolism is related to the androgen-oestrogen ratio in the plasma.

Summary

Plasma zinc concentrations rise in men over the age of 55 years and fall in women of a similar age-group. They are higher in men with clinically diagnosed benign prostatic hyperplasia, but the level does not appear to be related to the size of the gland. Plasma zinc concentrations are not helpful in the diagnosis or management of carcinoma of the prostate, but may prove useful in excluding this diagnosis.

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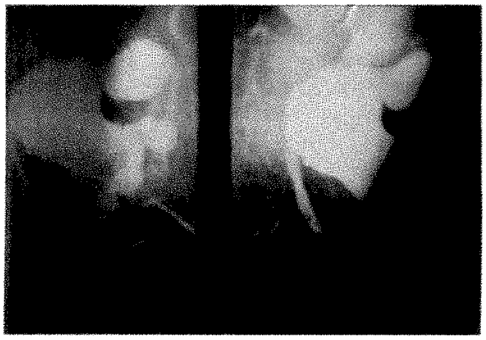
Short Case Report

Fallopian Tube as Ureteral Substitute in a Living Donor Renal Allograft

A 32-year-old woman received a living donor renal allograft in November 1971. 5 months post-transplantation, distal ureteral obstruction required lysis of adhesions and subsequent secondary ureteroneocystostomy. 7 months post-transplantation, release of ureteropelvic junction obstruction by VY-plasty was performed. 11 months post-transplantation, recurrent ureteropelvic junction obstruction was demonstrated by retrograde cystoureterography. Resection of the stenotic ureteropelvic junction and salpingopyelostomy was performed as a two-layer, end-to-end anastomosis. 1 week later disruption of the salpingopyelostomy occurred. Primary repair, stent placement and complementary nephrostomy were unsuccessful in avoiding stricture formation at the salpingopyelostomy site (Figure). The Fallopian tube was ultimately replaced with an ileal segment 14 months post-transplantation which has functioned satisfactorily to date.



Appearance of salpingopyeloureterostomy with salpingopyelostomy stricture.

Comment

The use of the Fallopian tube in ureteral substitution is recommended for its (1) anatomic proximity, (2) expendibility, (3) similarity to ureter—presence of a mucosal lining and peristaltic muscular wall, (4) manipulable blood supply and (5) availability as an autogenous graft. Fallopian tube ureteral substitutes have been shown to develop proximal hydronephrosis after 21 days.As demonstrated in this case report, anastomotic failure is also a problem.

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The Concentration of Sulphamethoxazole and Trimethoprim in Human Prostate Gland

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In chronic bacterial prostatitis most anti-microbial drugs are ineffective for eradication of the infecting organisms from the prostatic fluid. Dunn and Stamey (1967) detected only minimal diffusion of nitrofurantoin into prostatic fluid. Stamey, Meares and Winningham (1970) found that ampicillin, penicillin-G, cephalothin, kanamycin, oxytetracycline, polymyxin-B and nalidixic acid were nearly undetectable. Winningham and Stamey (1970) found an adequate therapeutic level of some sulphonamides in the prostatic fluid of the dog. Hessl and Stamey (1971) concluded from theoretical and experimental data that of the tetracycline derivates only tetracyclinehydrochloride, if administered intravenously, has the potential of achieving significant inhibitory concentration against Gram-negative bacteria in prostatic fluid. Their observations were in disagreement with those of Fabre *et al.* (1971) who found good concentrations of doxycycline in the homogenised human prostate gland.

At any rate one may conclude that the anti-bacterial arsenal for the treatment of chronic prostatitis is very restricted. In the following study we measured the concentration in human prostate gland of the combination of sulphamethoxazole (SMZ) and trimethoprim (TMP) in order to define its possible role in the treatment of chronic bacterial prostatitis. This combination is already widely used in the treatment of urinary tract infections.

Methods

Nineteen patients, suffering from benign prostate hypertrophy, received the drug combination before prostatectomy by enucleation. Their age varied from 59 to 81 years. Six of them received 400 mg SMZ+80 mg TMP by a single intramuscular injection about 4 hours before operation; 5 others received the drug combination in 2 tablets, each containing 400 mg SMZ and 80 mg TMP, also 4 hours before operation; the third group (8 patients) received 2 tablets 2 times a day, for 4 days, with the last intake some 4 hours before operation.

Blood-samples were taken at the same time as enucleation of the prostate. Prostate and blood samples were frozen immediately and kept at −20°C until just before analysis.

TMP was determined by the spectrofluorimetric method of Schwartz (Schwartz, Koechlin and Weinfeld, 1969; Schwartz, 1972) and free (active) and total sulphonamides by the method of Bratton and Marschall, modified by Rieder (Rieder, 1972).

Results

The SMZ and TMP determinations in plasma and prostate are listed in Table I.

The highest concentrations of SMZ and TMP are reached after the repeated dose. The prostate was better impregnated with SMZ after 4 days: the plasma/prostate ratio varied from 1·25 to 3·29.

Table 1

All concentrations are expressed in γ/ml. $\bar{X}$ = mean value.

	Time between last dose and prostatectomy	SMZ (active)			TMP			Prostate SMZ TMP
		Plasma	Prostate	Plasma Prostate	Plasma	Prostate	Plasma Prostate	
1 amp. intra-muscul.	5 h 35	12,1	3,16	3,82	0,41	0,81	0,50	3
	4 h 00	13,5	5,06	2,66	0,46	1,34	0,34	3
	4 h 00	23,2	6,51	3,56	0,51	1,67	0,30	3
	3 h 55	21,2	...	...	0,54	2,47	0,21	...
	2 h 40	18,2	5,33	3,41	0,22	1,67	0,13	3
	3 h 10	17,8	5,87	3,03	0,26	1,34	0,19	4
		$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =
		17,8	5,19	3,29	0,40	1,55	0,28	3,7
2 tablets	4 h 00	17,8	4,61	3,86	1,37	3,13	0,43	1
	4 h 00	27,1	13,40	2,02	0,93	3,17	0,29	4
	4 h 05	32,9	10,00	3,29	1,18	5,00	0,23	2
	7 h 30	30,6	...	...	0,97	2,41	0,40	...
	4 h 50	2,26	0,45	5,02	0,43	0,47	0,91	0,95
		$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =
		26,2	7,11	3,55	0,98	2,84	0,45	2
2 × 2 tabl/day during 4 days	3 h 45	108,2	50,1	2,15	2,53	5,84	0,43	8
	3 h 50	66,6	52,8	1,55	2,96	5,82	0,50	7
	3 h 55	40,8	15,2	2,68	1,91	5,09	0,37	2
	4 h 45	63,2	19,2	3,29	2,68	5,57	0,48	3
	4 h 25	58,0	23,6	2,45	1,73	4,11	0,42	5
	4 h 30	80,6	64,5	1,24	2,82	7,73	0,36	8
	5 h 20	43,4	...	...	0,73	4,29	0,12	...
	5 h 00	66,3	29,1	2,27	3,91	5,91	0,66	4
		$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =	$\bar{X}$ =
		65,9	34,9	2,23	2,39	5,54	0,42	5,3

TMP is 2 to 3 times more concentrated in the prostate than in the plasma. These high concentrations are reached already after 4 hours.

After 4 days of treatment the SMZ/TMP ratio varied from 2 to 8.

Discussion

Research seems to show that the concentrations of SMZ and TMP, measured in the enlarged, enucleated prostate are representative for the concentrations of both products in the acini of the prostate gland in adult men.

The factors determining diffusion into the prostate gland (lipid solubility, pKa and degree of ionisation, protein binding) are excellent for TMP (Stamey *et al.*, 1970). Reeves and Ghilchik (1970) were the first to draw attention to the high concentrations of TMP (2 to 3 times higher than in serum) in the prostate fluid of the dog. Robb *et al.* (1971) affirmed these experiments and found concentrations as high as 16,2 times the plasma levels. Granato, Gross and Stamey (1973) obtained comparable results. They suggest that factors, other than non-ionic diffusion may also regulate TMP concentration in the prostate fluid of the dog. TMP concentrations in human prostatic tissue and prostatic fluid were first measured through a microbiological method by Nielsen and Hansen (1972). They found the concentrations of TMP "at a therapeutically active level with respect to the majority of those bacteria usually occurring in urinary tract infection". We found TMP concentrations in the human prostate 2 to 3 times higher than in the plasma.

Winningham and Stamey (1970) and Robb *et al.* (1971) found a plasma concentration of SMZ 10 times higher than that of prostatic fluid. The prostate concentration of SMZ in our study was more favourable. The ratio of plasma concentration to that of prostate varied from 1·2 to 5·0.

Carroll *et al.* (1971) established the antibacterial effectiveness of the SMZ-TMP association in the prostate fluid of the dog and suggested the possibility of therapeutic application to chronic bacterial prostatitis. Schirren and Schaller (1971) reported on the prolonged high concentrations of SMZ/TMP in the human seminal fluid.

Although we found high concentrations of TMP in the prostate, its ratio to SMZ is not optimal. Nevertheless the ratio SMZ/TMP is sufficient to obtain a synergism of both components against a wide variety of micro-organisms and especially Gram-negative bacteria (Böhni, 1969*a*, *b*).

The relevance of our results in association with other data of the literature for the treatment of bacterial prostatitis seems obvious. However, communications mentioning clinical trials of SMZ/TMP in bacterial prostatitis are rather seldom. Stamey (1972) wrote about 13 patients of whom 2 seemed to be cured after 14 days of therapy. Hirdes and Schönfeld (1973) described excellent results in 25 of 32 patients. In our department a clinical trial is now in progress.

Summary

Sulphamethoxazole and trimethoprim concentrations were measured in 19 enucleated human prostate glands.

Good concentrations of sulphamethoxazole were found after 4 days of treatment: the ratio of plasma concentration to that of prostate varied from 1·25 to 3·29. The trimethoprim concentrations were 2 to 3 times higher in the prostate than in the plasma. These high concentrations were reached very rapidly after the first dose of trimethoprim.

The results are compared with data from the literature.

The combination sulphamethoxazole-trimethoprim should be of value in the treatment of bacterial prostatitis.

We wish to thank Prof. Rieder, Department of Experimental Medicine, F. Hoffmann-La Roche and Co. Ltd, Basle, for his technical co-operation in ensuring the determination of SMZ and TMP in the prostate gland.

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Management of Complete Disruption of the Posterior Urethra

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Although the treatment of a stricture following complete disruption of the posterior urethra has been greatly improved by various plastic procedures, prevention of this complication is to be preferred. Mitchell (1968) believes that a stricture always follows a complete disruption, but some good results, without strictures, after primary repair have been reported (Myers and De Weerd 1972, Pierce 1972). Large series, however, have not been presented because total disruption is relatively rare. One of the largest trauma clinics in our country reported an average of 1 case a year (Gallas, 1968) and Mitchell (1968) had only 2 cases out of a series of 60 urethral injuries.

A simple method of direct approximation of the ruptured ends of the urethra by perineal traction (as mentioned before by Leadbetter, 1945; Kisner, 1958; Pierce 1972; Turner Warwick, 1972) has been used by us during the last 6 years. As previous authors did not report their results, we would like to present our technique and results.

Diagnosis

In cases of a fractured pelvis when blood is coming from the urethral meatus or when the patient is unable to micturate, we try to pass a Tiemann catheter. Unsterile and rough handling can of course result in infection and more damage to the urethra. Contrary to Mitchell (1968), however, we are not afraid of contamination of the retropubic space, because inability to pass the catheter leads to operation and drainage. Partial ruptures, when a catheter can be passed into the bladder, are treated by catheter drainage for 2 or 3 weeks. When no urine comes through the catheter, water-soluble contrast fluid is injected through the catheter. Irregular filling of the retropubic space can easily be seen on the X-ray film. When a bladder or urethral injury is suspected some prefer to do an intravenous pyelogram. A total disruption is diagnosed when the bladder is shown pulled up and has a teardrop configuration (Fig. 1). We do not routinely perform either an IVP or introduce contrast up the catheter, for once a catheter has been passed and no urine is obtained an operation is performed within a few hours to avoid the formation of infected blood (and maybe some urine) in the retropubic space.

Treatment

Total disruption does not require acute treatment. Because the prostate is displaced upwards, the bladder neck is closed. Therefore very little or no urinary leakage occurs. Vital problems such as shock must be corrected first. There is ample time for therapeutic and diagnostic measures.

When considering repair of a ruptured posterior urethra one can choose between 5 different procedures: (1) Retropubic end-to-end anastomosis; (2) Perineal end-to-end anastomosis; (3) Cystostomy and delayed urethroplasty; (4) Simple traction by balloon catheter; (5) Perineal traction on the prostate.

The stricture is the result of a gap between the 2 ruptured ends of the urethra. If this gap is filled with fibrous tissue it ultimately results in stricture formation. To prevent this the muscular layers and adventitia of the urethra must be brought into contact; epithelialisation will then follow secondarily. All authors agree, therefore, that the best prevention of a stricture should be direct approximation of all layers of the ruptured ends. Primary anastomosis—retropubic or perineal—

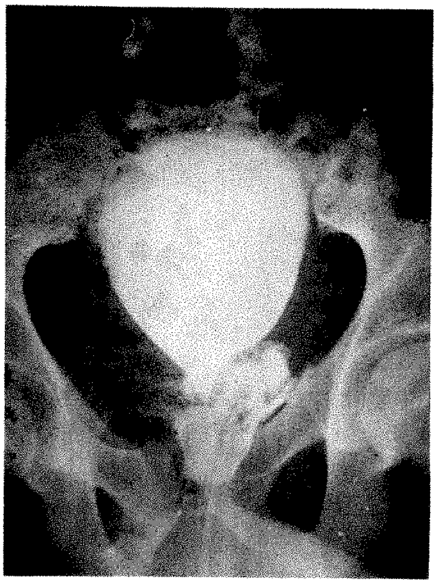

Fig. 1. Combination of IVP and catheter-filling in complete disruption of urethra. Typical teardrop appearance of the bladder on IVP and extra-vesical contrast by catheter.

is, however, technically difficult or impossible. The retropubic approach does not give a good view; profuse bleeding from the fractured pelvis restricts vision in the lower pelvis, and in the bloodstained and broken urogenital diaphragm the shredded end of the urethra is not clear. The perineal approach gives a better vision and reasonable results but is often not possible in the patient with multiple injuries. It is often a major operation with an abdominal and perineal stage. Those that believe a stricture is inevitable, perform secondary plastic procedures (Morehouse, Belitsky and McKinnon, 1972) after a primary simple cystostomy. But the disadvantage of this method is the long period of treatment, often with multiple operations. Complications after the various plastic procedures are often seen (Whitehead and Morales, 1972). Furthermore healing of a total disruption without any form of approximation results in a long and difficult stricture (Turner Warwick, 1973).

Simple balloon catheter traction has some major disadvantages and should not be used. No one can indicate the right amount of traction that must be given. If the traction weight is not enough there remains a gap between the 2 ruptured ends resulting in a stricture. If the weight is too great it results in necrosis of the bladder neck and/or the bulbous urethra. As for the bladder neck, we may need this later on for continence in case a urethral stricture of the membranous urethra requires correction with destruction of the external sphincter (Turner Warwick, 1973). All continence then depends on the bladder neck.

As for the urethra, some mention traction on the catheter with an angle of 45 degrees to avoid necrosis by pressure, but too heavy traction may result in a urethral fistula. The results obtained by this method are generally less satisfactory than those with one of the other methods (Gallas, 1968).

For these reasons we tried direct repair by traction on the prostate.

Technique

The patient is put on the operating table with the legs spread as wide apart as the table permits. Perineum, penis and scrotum are disinfected, together with the lower abdomen. This whole area is included in the operating field.

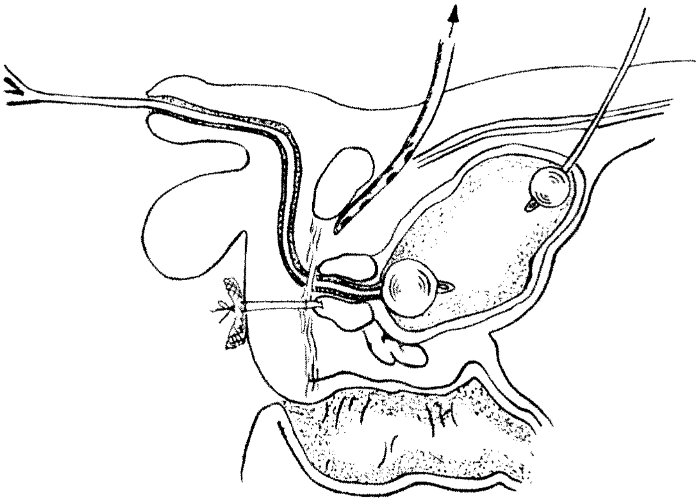

Fig. 2. Treatment by prostate-traction.

Through a lower abdominal incision the retropubic space is exposed. Blood and bloodclots are removed. To make sure no intestinal injury is overlooked the peritoneum is briefly opened and if no free fluid or blood emerges, it is immediately closed again. In complete disruption the prostate is obviously dislocated upwards. The distal ruptured end of the urethra cannot be located as it is situated in the fragmented and bleeding urogenital diaphragm.

A Dufour catheter Ch.22 with a 40 cc balloon is introduced through the penis and can be retrieved in the retropubic space. The bladder is then opened. When no IVP has been done before operation the function of the upper urinary tract is checked by intravenous injection of frusemide and indigocarmine. After a few moments jets of blue can be seen coming from the urethral orifices. A Nélaton catheter is passed from within the bladder through the bladder neck into the retropubic space, where it is attached to the Dufour catheter which is now pulled into the bladder.

The traction sutures on the prostate are then inserted: a chromic catgut suture (size 4-0 or 5-0) is passed through each lateral lobe. Each suture is now put with both ends on a long straight Réverdin needle. The needle is passed through the urogenital membrane as close to the Dufour catheter as possible to emerge on each side of the perineum. At this stage the sutures are left hanging loose.

To complete the operation the bladder is closed; with suprapubic drainage by a balloon catheter. The 40 cc balloon of the Dufour catheter is inflated fully, so that the big balloon can be used for 24 hours to pull on the bladder neck. This is in addition to the traction sutures to prevent blood accumulating between the 2 ruptured ends.

A drain is placed in the retropubic space and the wound is closed. The perineal sutures are pulled tight, so that the prostate is fixed against the fragmented urogenital diaphragm and tied over a rolled-up gauze (Fig. 2). The Dufour catheter is also pulled tight so as to splint the urethra straight and is tied to the upper thigh of the patient with an elastic band.

In the postoperative period the patient is given an antibiotic, at first intramuscularly, later orally. After 24 hours the elastic band of the Dufour catheter is released. This catheter is chosen because it has a large opening at the end and side openings, which makes blockage of the catheter by blood clots or encrustations less likely. The bladder is flushed daily through one of the draining catheters. In future a fenestrated catheter may be of help to evacuate urethral discharge (Turner Warwick, 1973).

The chromic catgut sutures are removed after 10 days and the Dufour catheter after 3 weeks. Now the cystostomy catheter is closed off and the patient may attempt to urinate. If there is difficulty in urination, retention of urine or incontinence, the cystostomy catheter is left open for another week and the procedure repeated.

Usually, normal micturition is restored after 4 or 5 weeks. A control urethrogram is first made after 6 to 8 weeks. The urine usually becomes clear of leucocytes after 8 to 10 weeks.

Results

We have operated on 7 patients in this way since the beginning of 1968, being dissatisfied with catheter traction at that time.

One patient, a man of 71 years old, died 4 weeks after the operation because of other injuries obtained in the accident. He was urinating normally.

No patient has had a stricture so far. To be safe the first patient was dilated during the first 3 months, but has had a normal micturition since June 1968.

A favourable condition was the fact that all patients were operated upon within a few hours of the accident, so that no contamination of the retropubic space could occur, which could otherwise have resulted in secondary wound healing with stricture formation.

We think that direct correction of the total disruption of the urethra is a very useful technique. Mitchell (1968) mentions a minimum follow-up of 5 years and preferably 10 years before we can speak of a definite result; we have 2 patients with a follow-up of more than 5 years, but we thought it was reasonable to report the other patients also.

Finally, any stricture forming after this method has been applied is very short and should be directly correctable by excision and end-to-end anastomosis.

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Vas Anastomosis: a Return to Simplicity

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The widespread use of vasectomy for elective sterilisation has resulted in an increasing number of requests for restoration of fertility. The author has been successful in restoring sperm to the ejaculate by vasovasostomy in at least 80% of 117 cases. Pregnancy has followed in the wives of 30% of these men.

Many techniques have been proposed to facilitate the operation and to improve its outcome (Schmidt, 1956, 1961), but most of these innovations are no substitute for simplicity. Anastomosis of the vas is comparable to most other anastomoses, but it presents problems of its own which must be understood if it is to be successful.

Anatomical and Pathological Conductions

The vas deferens arises from the epididymis as a convoluted duct. Its convolutions are tortuous and sometimes it even doubles back upon itself. As it progresses, it gradually straightens and its wall thickens (Fig. 1). The location of the proposed anastomosis is determined of course by the site of the original vasectomy: optimal when in the straight vas with no significant defect in its length, less favourable in the convoluted portion. The operation is impossible when substantial lengths of vas have been resected.

After vasectomy, the lumen of the proximal (testicular) vas dilates, thus thinning its wall (Schmidt, 1959) (Fig. 1). The outside diameter of the vas remains the same but the diameter of the lumen enlarges 2 to 4 times: the anastomosis, therefore, must join lumens of different sizes.

In addition, the original vasectomy results in scarring of the *sheath* of the vas. This sheath facilitates spontaneous anastomosis (Rolnick, 1924). Most research on vas anastomosis is conducted by dividing the vas, then immediately anastomosing it with the sheath intact. In clinical practice, both the scarring of the sheath and the dilatation of the lumen make for different and more difficult conditions.

Surgical Principles

The best anastomosis is that which most simply approximates the opposing layers of tissue—consequently, the principles of *end-to-end, mucosa-to-mucosa* anastomosis are followed. Because of the thick walls of the vas, oblique cuts lack the advantages (greater circumference and area) seen in the thin-walled ureter. Thickness of the walls permits the anastomosis to be performed with only a few sutures. For the same reason, kinking of the vas does not occur, thus stents are not necessary.

Stricture of the vas appears to be unimportant—pregnancies often occur after spontaneous anastomoses of minute diameter.

The ends of the vas must be approximated without tension, a special problem when they are some distance apart and the weight of the testis is upon the anastomosis. The supporting fascial sheath must be sutured, so that the vas ends cannot be pulled apart, even with mild traction (Fig. 2).

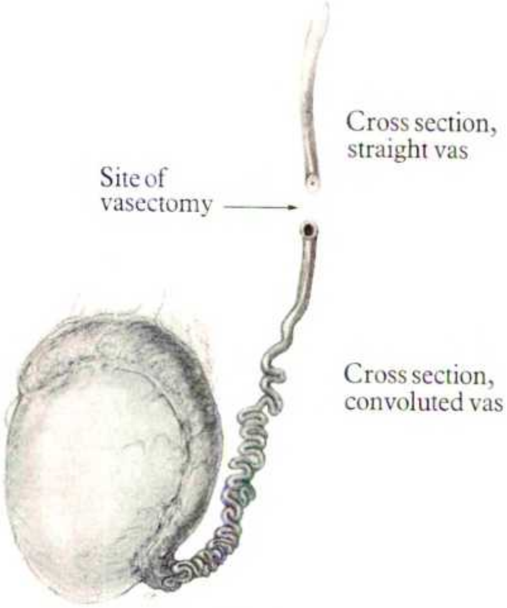

Fig. 1

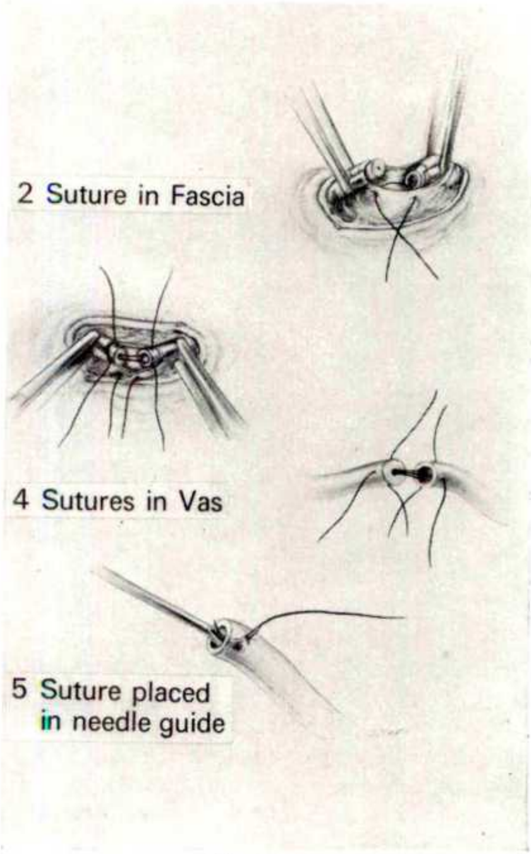

Fig. 2, 4, 5.

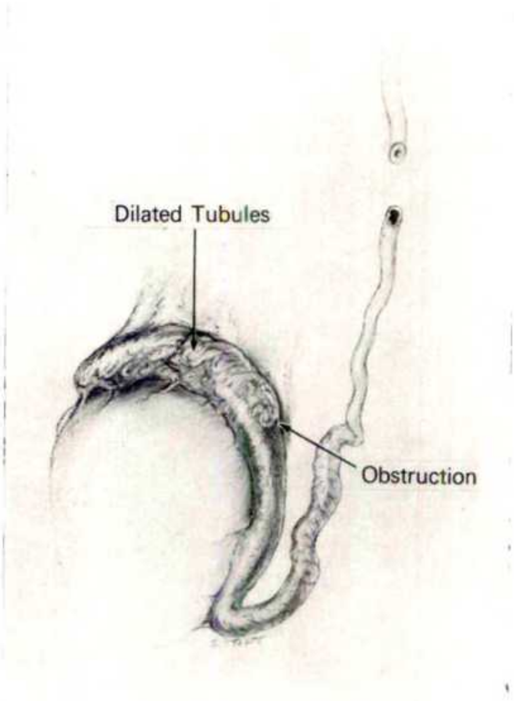

Fig. 3

Fig. 1. Convoluted and straight vas with cross-sections showing wall thickness of proximal and distal vas. Note optimal site of vasectomy—in straight vas.

Fig. 2. Sketch of fascial suture.

Fig. 3. Obstructed epididymis with dilated seminiferous tubules.

Fig. 4. Sutures in vas.

Fig. 5. Needle guide and guide in use.

The actual anastomosing sutures are responsible for approximating the layers of the vas wall and for making the anastomosis "watertight". Non-reactive, monofilament sutures of fine diameter are best. They should be placed through the entire thickness of the vas wall, into the lumen. Because of the thickness of the wall, these sutures create a tight, leak-proof anastomosis, making stents and splints[1] unnecessary; fibrin and clot rapidly seal the anastomosis.

The vas must be sutured with precision. Optical aids are a great advantage. The author uses a loupe (magnification 2½) when freeing the ends of the vas and when placing the fascial sutures, and the operating microscope (magnification 10 to 16) while placing the anastomosing sutures.

Technique

The operation is best done under light general anaesthesia on an out-patient basis: hospitalisation is unnecessary.

The point of interruption can usually be palpated as a defect in the vas. One can often feel the nodular thickening of a spermatic granuloma or of vasitis nodosa of the proximal vas (present in approximately 23% of patients).

A 3 to 4 cm incision is made in the scrotum. The fascia of the scrotum is spread apart so that the vas can be grasped with Allis clamps above and below the point of obstruction. Longitudinal incisions are made in the sheath of the vas down to, but not entering, the vas. Transverse cuts are then made to freshen the ends, care being taken to conserve all possible length. Only if a spermatic granuloma is found is it necessary to resect the scarred end of the vas. The underlying fascia is freed for 2 to 3 mm from each end to prevent its being interposed in the anastomosis.

Patency of the distal vas is determined next by injecting normal saline solution into it through a blunted 23 gauge hypodermic needle. This is done easily if no obstruction exists. When obstruction does exist, its site can be determined by probing with a 2–0 nylon suture. Patency of the proximal vas is proven by the appearance of spermatic fluid. This fluid will be either clear or milky; it may lack sperms, show only sperm heads or show motile sperms. Once released, it often continues to flow and must be removed from the wound by sponging or by irrigation. If no fluid can be expressed by milking the vas, one should expose and inspect the epididymis: in 10 to 20% of all patients, an obstruction will be found; dilated tubules, either patchy or extending partly down the epididymis will be seen with the naked eye (Fig. 3). For such cases an epididymovasostomy can be tried.

When sperms are found in either vas, the outlook is excellent for sperm to appear in the ejaculate. Among the cases cited (Table II) only 2 of 8 failures showed sperm at operation.

When the vas is shown to be patent, a single suture of 4–0 nylon is placed in the fascia to approximate the vas ends (Fig. 2). This suture is held and tied only after the anastomosing sutures are placed in the vas and tied.

Next, 3 sutures are placed (Fig. 4) at 120° intervals through the full thickness of the vas, using preferably Ethicon 8718-H, a 6–0 polypropylene suture with needles at both ends which permits the needles to be placed into the lumen on each side and then out through the vas walls. It is important to place the first 2 sutures posteriorly, next to the fascial suture since this is the point of potential leakage, being hidden after these sutures are tied. The upper suture is placed last. Additional sutures, not entering the lumen, can be placed anteriorly if necessary. Bonney clamps, modified by shortening the tubular portion to ⅜″, are excellent for holding the vas ends while placing these sutures.

If double-armed sutures are not available, single-armed sutures can be used, with a needle guide marking the lumen and thus preventing the needle from crossing and obliterating the lumen (Fig. 5). This needle guide also holds the vas firm, permitting easy insertion of the suture needle.

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[1] The use of endosplints in vas anastomosis has proven less than satisfactory: the splints are often displaced and apparently extruded out through the vas and ejaculated. For that reason the author has abandoned this technique.

Table I
Vas Anastomosis Follow-up

Questionnaire (sent Autumn, 1973)	Number of Cases	Per Cent
Answers	37	69·8
No answer	16	30·2

Additional fascial sutures can be placed over the anastomosis, and the skin is then closed. A sterile dressing and a scrotal support are applied. The support is worn for 14 days to immobilise the scrotum. Bathing is permitted after 48 hours and sexual intercourse may be resumed in 10 days. Testing for sperm is commenced after 1 month.

Reason for Failure

1. One or both epididymides will be found to be obstructed in 10 to 20% of patients: epididymovasostomy may then be attempted, but its success rates are poor.
2. In some cases an excess of vas will have been resected, making uniting of the ends impossible.
3. Leakage from the anastomosis can result in the formation of a spermatic granuloma. The inflammation and scarring associated with this lesion may obstruct the anastomosis. If, for this or any other technical reasons the operation fails, it can be attempted again with good hope for success.
4. Scarring can occur at the point of emergence of a splint (Fernandes, Shah and Draper, 1968), an additional reason for not using one.
5. Postvasectomy autoimmunity to sperm often occurs (Ansbacher, 1973). The spermatic granulomas frequently present after vasectomy deposit spermatic protein into the tissues. This extravasation appears to be directly related to antibody level (Alexander, 1973).

The role of sperm autoimmunity in causing sterility is still vague. Two different antibodies have been described. Their effects can sometimes be seen upon semen examination under the microscope. When an immobilising antibody exists, all sperms appear non-motile and thus dead. When the agglutinating antibody is present, the sperms are actively motile but are clumped so that they are unable to separate from one another and to move normally (Fig. 6).

Prevention of autoimmunity to sperm is tied to the prevention of sperm spillage: consequently, the vas is sealed at the time of vasectomy as a measure against the development of spermatic granuloma, and sperm spillage is carefully avoided at vasovasostomy. Prednisone may be useful in overcoming this immunity: the author and other urological surgeons (Charney, 1973) have seen cases improved by the administration of this drug, but further evidence corroborating their experience is necessary. Possibilities for treating the seminal fluid itself have not been explored; however, Schoysman reports that freezing and thawing released sperm from agglutination (Schoysman, 1973).

A marked discrepancy exists between success as judged by sperm appearing in the ejaculate (patency) and as judged by pregnancies (fertility). After the operation, sperm counts are often low and sometimes sperm do not appear until months later. Two reasons for these phenomena are possible: (*a*) After vasectomy, the tubules of the epididymis dilate. Their walls are thin and, when dilated, become even thinner. Just as a chronically dilated ureter seldom regains its tone or its ability to peristalse after obstruction is corrected, the epididymis may be the site of a similar condition—slowing sperm transport and causing many sperms to die before they reach the vas; the epididymis, in other words, has become *adynamic*. (*b*) After vasectomy, balance is reached between sperm production and sperm absorption. Phagocytosis accounts for sperm absorption

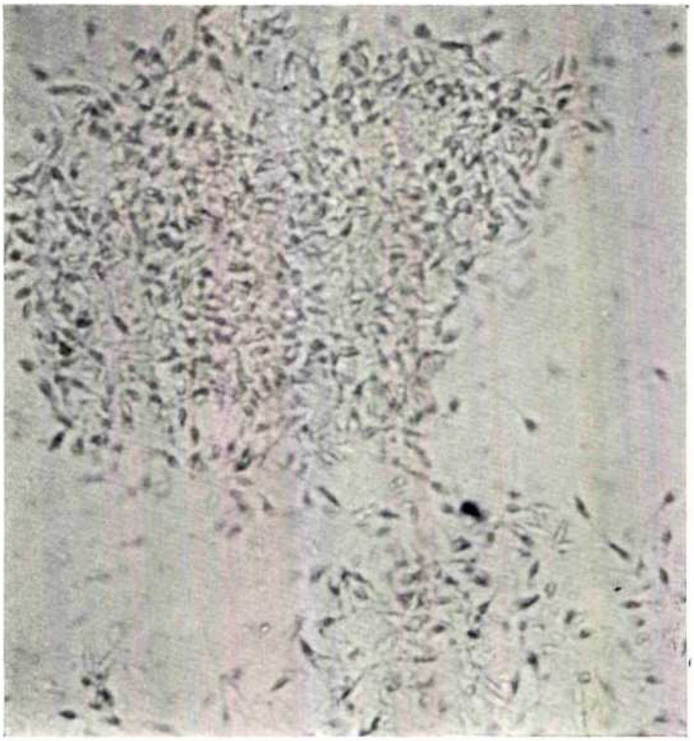

Fig. 6. Agglutinated sperm.

Table II

Results of Vas Anastomosis

18 months' results by techniques described (53 patients)	Number of Cases	Per Cent
Never tested postoperatively	9	
Tested postoperatively (some information)	44	
Sperm	36	81·8
No sperm	8	18·2
Pregnancies	8 (to date)	16
Failures	8	15·2
No sperm found at operation	5	9·5
Sperm found at operation	2	3·8
Not tested at operation	1	1·9
Spermatic granuloma of vas	12	22·6
Previous 4-year results by various methods (64 patients)		
Pregnancies	20	31
Sperm and/or pregnancies	50	78

and is far more active than in the normal. Phagocytosis may also remain hyperactive so that only few sperms escape it. In these cases and in those of autoimmunity, the operation is a technical success but pregnancy does not ensue.

One peculiar circumstance frequently accompanies the anastomosis: follow-ups may be difficult to secure. As a rule, the operation is done during a second marriage, often to please the new wife, and the man is more or less indifferent about its success. He feels that he has done his part by undergoing the operation—and many a man rejects testing, for he fears a failure that would force him to undergo further surgery or that might disrupt his marriage. As shown in Table I only about 70% of the patients of the cited series (Table II) answered a questionnaire sent in 1973. Information on others was secured at different times.

Summary

Vas anastomosis is successful in restoring sperm to the ejaculate in 80 to 90% of cases.

A *simple*, end-to-end, mucosa-to-mucosa anastomosis performed with non-absorbable, monofilament sutures is, in the author's opinion, the best procedure.

Pregnancies follow in about one-third of the cases.

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Kaposi's Sarcoma of the Penis

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Kaposi's sarcoma is not commonly seen in non-African countries, but with the increase in travel, "rare" diseases may be seen far from their normal habitat. Kaposi's sarcoma of the penis is extremely rare; only 12 cases have previously been recorded (Hayes, 1971). Of these, only 9 involved the glans penis, but a 10th such case was reported by Summers (1972). An 11th case is now added, which is also of interest in that a correct preoperative diagnosis was made.

Case Report

A 40-year-old Bantu patient was admitted from a rural clinic which he had attended complaining of swelling of his penis which had been present a few weeks. The doctor who referred him considered that the lesion might be a carcinoma.

The patient was well-nourished and not in pain. He gave no history of haematuria or other symptoms of urinary tract disease.

Physical examination showed slight bleeding, and a moderate purulent discharge from beneath a swollen prepuce. The latter could be retracted sufficiently to reveal a red raised nodule, 2 mm high and 10 mm in diameter, on the right side of the glans penis. There was no significant inguinal lymphadenopathy, and general examination was negative, except for the right foot. This was mildly oedematous, with nodules typical of Kaposi's sarcoma (Fig. 1).

Because the lesion of the glans penis did not resemble the florid, papilliferous carcinoma of the penis commonly seen in Central Africa, and of the other evidence of Kaposi's sarcoma, a provisional diagnosis of Kaposi's sarcoma of the glans penis and right foot was made. Radiography of the right ankle and foot showed "an area of translucency just above the distal end of the tibia, with a depression on the lateral aspect. There is considerable bone absorption in the fifth metatarsal, and rather less in the third and fourth. There is also absorption of bone in the proximal phalanges of most toes. The appearances are compatible with Kaposi's sarcoma."

Biopsy of the skin nodules and excision biopsy of the lesion of the glans penis were carried out.

Histological examination of the specimens from the foot showed a fibroblastic angiomatous tumour in the deeper dermis with considerable cellular pleomorphism and mitotic activity (Figs. 2 and 3).

Histological examination of the penile tumours showed that the lesion was fibroblastic, being composed of whorls of spindle cells in an angiomatous stroma, in which there were areas of red cell extravasation and haemosiderin deposition (Fig. 4). Higher power examination showed sarcomatous features with nuclear pleomorphism (Fig. 5).

1 year later the patient showed no evidence of recurrence of the penile lesion, but has since been lost to follow-up.

Discussion

Involvement of every organ except the brain has been described in patients with Kaposi's sarcoma (Davey, 1968). But even in Bantu patients in whom the incidence of this tumour is about 10 times that in Caucasians (Oettle, 1962), involvement of structures other than the skin, in the earlier stages, is uncommon, and involvement of the penis, even when the disease has become generalised, is extremely rare. Hayes *et al.* (1971) reported a case involving the glans penis, and found 8 similar cases in the literature and 4 other cases affecting the shaft of the penis. They quote Philippson (1902), who described a case in which the initial lesion on the glans penis had not recurred 8 years after local excision although generalised cutaneous lesions had appeared at 4 years. Summers *et al.* (1972) found 9 cases involving the glans penis in the literature, and reported another in a 60-year-old Italian.

In Africa, Kaposi's sarcoma follows a geographic distribution similar to that of Burkitt's lymphoma, which is a disease of the reticulo-endothelial system (Oettle, 1962). It accounts for

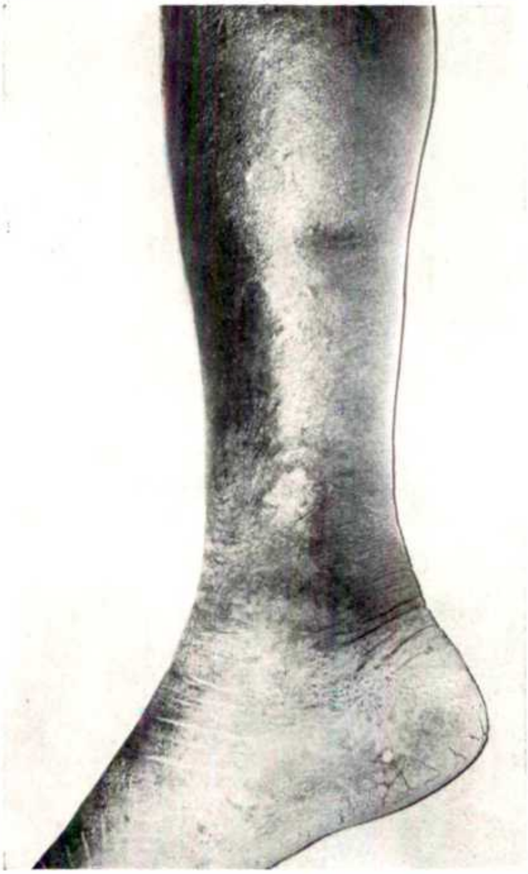


Fig. 1. Right foot showing nodules typical of Kaposi's sarcoma.

10% of malignancies in natives of the Congo and a large proportion in the Bantu of Southern Africa (Rothman, 1962; Davies, 1962), but is unusual in American Negroes (Herring, 1963). It was originally considered to be confined to the Jewish and Italian races, but Bluefarb (1957) documented its occurrence in all major ethnic groups.

All the evidence suggests that Kaposi's sarcoma is linked to a generalised disorder of the reticulo-endothelial system (Dayan *et al.*, 1967). This would suggest that treatment of local lesions should be conservative. The tumour is known to be radio-sensitive, and responds well to local perfusion with Methotrexate. A 10-year survival without treatment, and showing no change, is recorded (McCarthy and Pack, 1950).

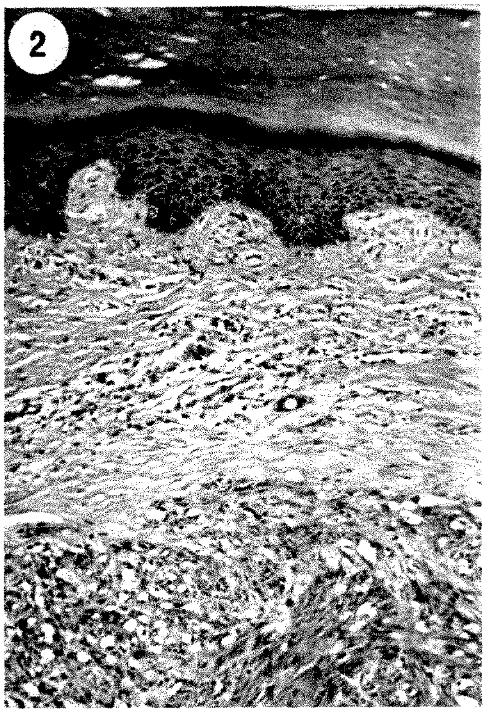
The preferred treatment of a penile lesion would therefore seem to be conservative, by local excision, possibly supplemented by a small dose of irradiation. Summers *et al.* (1972) suggest

Fig. 2. Skin from dorsum of foot. A fibroblastic angiomatous tumour in the deeper dermis. H & E. ×80. (See right)

Fig. 3. Skin from dorsum of foot. High power of tumour in Figure 1. There is considerable cellular pleomorphism and mitotic activity. H & E. ×200. (See right)

Fig. 4. Penile tumour. The lesion is fibroblastic, being composed of whorls of spindle cells in an angiomatous stroma in which there are areas of red cell extravasation and haemosiderin deposition. H & E. ×32. (See right)

Fig. 5. Penile tumour. High power of Figure 3, showing sarcomatous features with nuclear pleomorphism. H & E. ×200. (See right)



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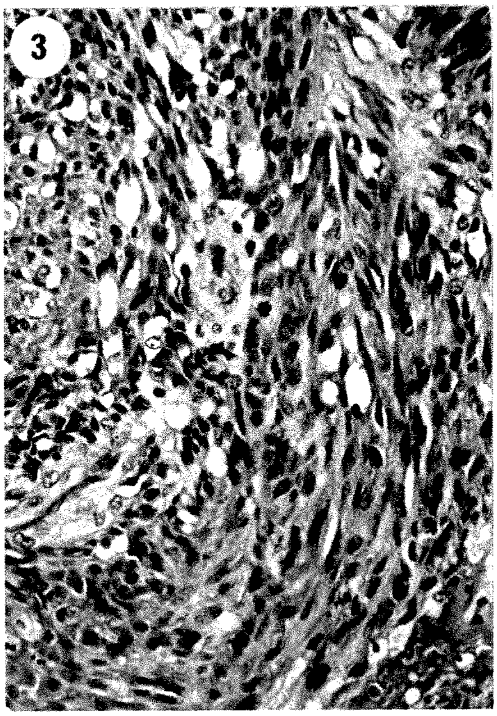

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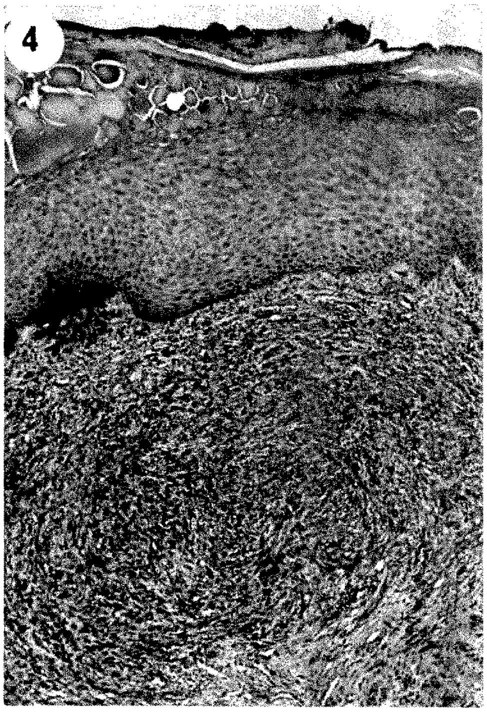

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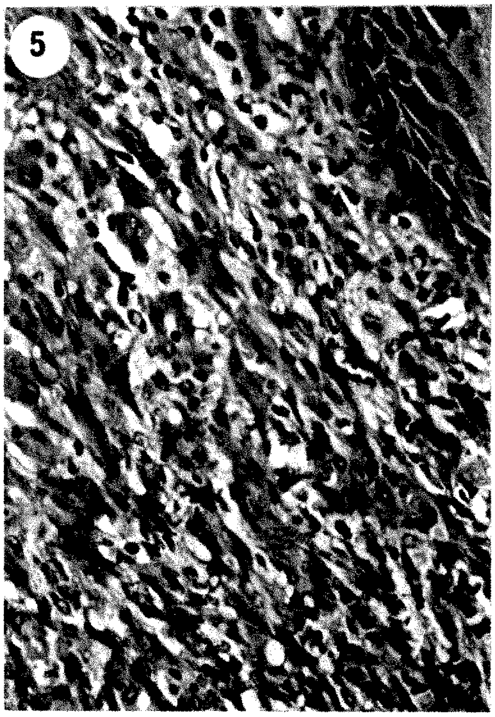

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1,800 R. Although Hayes *et al.* (1971) favour radical measures, and advise amputation on the basis of rapid recurrence after 6,000 rads in their case, our experience supports the adoption of a very conservative approach. It should be emphasised that local application of 5-fluorouracil is without effect in our experience.

Summary

The 11th case of Kaposi's sarcoma of the glans penis is reported. Aetiology and treatment are discussed and evidence adduced to support a conservative surgical approach by local excision, supplemented if necessary by low dosage irradiation and possibly methotrexate infusion.

I should like to thank Dr Andrew Watson for the radiological report, and Dr Alan Mills for the histological reports and microphotographs.

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Leiomyosarcoma of Penis—Case Report and Review of the Literature

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Leiomyosarcoma of penis is a very rare malignant tumour. Only 10 cases have been described in the English literature. A further case is reported and the previous cases are reviewed.

Case Report

An 84-year-old man was admitted to Dudley Road Hospital in June 1973, with 6 weeks' history of bleeding from a small lump in his prepuce. The lump had been present for some time (but the exact duration is not known) and it was mainly because of ulceration and bleeding that he attended his doctor who referred him for specialist opinion. There were no urinary symptoms. There was no relevant past medical history.

General and systemic examination showed no significant abnormality. Local examination revealed a small sessile, ulcerated papillomatous mass at the junction of the prepuce and glans penis on the postero-lateral region of the coronal sulcus. The mass bled when the prepuce was retracted. The lesion was diagnosed clinically as a carcinoma of penis. No enlarged inguinal lymph nodes were palpable.

Pre-operative investigations, including haematology (Hb and full blood count), chest X-ray and MSU for routine bacteriology were found to be normal.

Partial amputation of the penis was carried out. The postoperative period was uneventful and the wound healed satisfactorily.

Histopathological Features

Macroscopic. Penis 6 cm in length and 2 cm in diameter, with a raised ulcerated tumour 1·5 × 1 × 1 cm on the postero-lateral aspect of the glans. The growth was adherent to the prepucial skin. Its surface was homogenous, greyish-white, without obvious areas of haemorrhage or necrosis (Fig. 1).

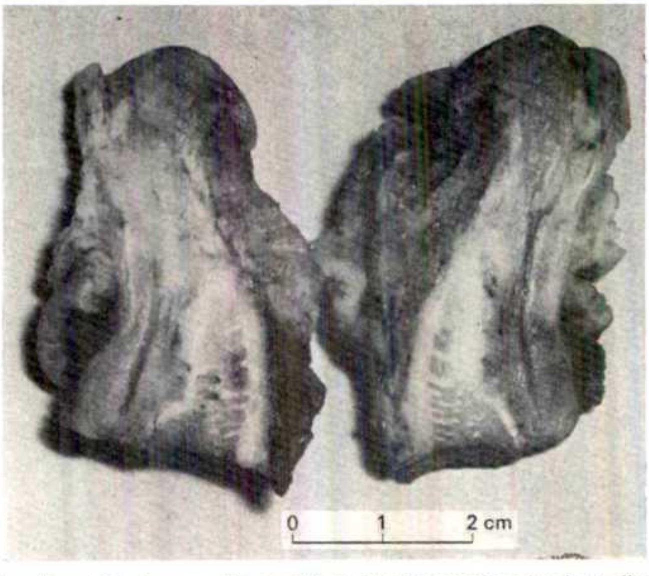

Fig. 1. Cut surface of the tumour. The partial amputation specimen has been sliced in half.

Microscopic. The overlying squamous epithelium was ulcerated. The tumour consisted of interlacing, sometimes whorled, bundles of spindle cells with blunt ends. There was moderate nuclear pleomorphism, with a few mitoses but no bizarre giant cells. Necrosis was absent (Fig. 2). The deeper connective tissue layers were invaded by the tumour, but no tumour cells were seen in the blood spaces of the corpora cavernosa. Special stains, *e.g.* phosphotungstic acid haematoxylin (PTAH), Masson's trichrome and Van Gieson, confirmed the presence of longitudinal myofibrils and the diagnosis of leiomyosarcoma arising from the smooth muscle of the penis was made.

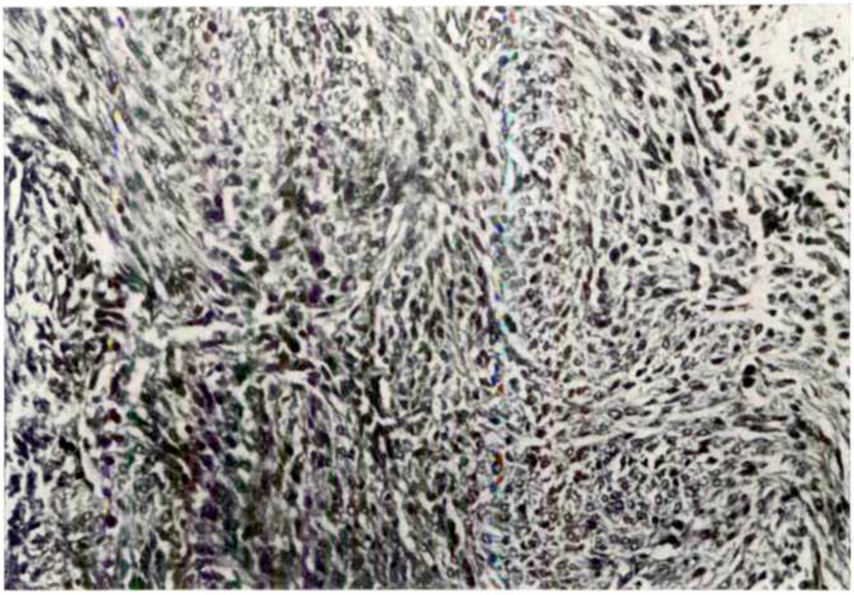

Fig. 2. Photomicrograph showing whorling pattern. × 180.

Progress

No postoperative irradiation was given. The patient was reviewed at 3-monthly intervals. He developed Klebsiella infection of the urinary tract 3 months after operation, but it cleared up on antibiotic treatment. He has remained well and free of metastases for 6 months.

Discussion and Review

Incidence. This present case is the 11th recorded example of leiomyosarcoma of the penis. A brief comparative description is given in the Table. Ashley and Edwards described the 4th case in 1957 and discussed fully the previous 3 cases (Levi, 1930; Kreibig, 1931; Meller, 1932). In their review of 54 cases of sarcoma, they found 8 cases of leiomyosarcoma of the urogenital system, 3 of which arose from the penis. In the 46 cases—including 8 cases of leiomyosarcoma—of sarcoma of the urogenital system reported by Tripathi and Dick (1969), not one was found to arise from the penis.

Age. The ages of the patients range from 6-84 years, but the majority (5 cases—Table) are aged 60 or more years. With the exception of a single case (Glucker, Hirshowitz and Gellei, 1972) aged 6 years, the remainder occurred between the 3rd and 5th decades.

Site. Five of the tumours occurred in the shaft, usually on the dorsum (Levi, 1930; Kreibig, 1931; Meller, 1932; Ashley and Edwards, 1957; Pack, Trinidad and Humphreys, 1963). The glans (Chaudhuri and Subrahmanyan, 1966; Glucker, Hirshowitz and Gellei, 1972) and root (Fagundes, *et al.*, 1962; Chaudhuri and Subrahmanyan, 1966; McKenzie Pratt and Ross, 1969) of the penis came next in order of frequency.

Diagnosis. The diagnosis is rarely made before biopsy. In most patients, as in the present report, a preoperative diagnosis of carcinoma is made, but sarcoma should be suspected if the tumour is of large size or fleshy consistency and contains areas of haemorrhage, necrosis and cystic degeneration (Pack *et al.*, 1963; Chaudhuri and Subrahmanyan, 1966).

Histopathological Features

Macroscopic. The tumours are described as ranging in size from a "small nodule" to a "small mass", the largest measuring up to 4 cm in length (Meller, 1932; Pack *et al.*, 1963). The colour is described as pale pink, fleshy, pinkish-brown, greyish and whitish (Table). The cut surface is usually homogenous with areas of haemorrhage and necrosis in the larger masses (Pack *et al.*, 1963; Chaundhuri and Subrahmanyan, 1966; Bakken, Hanna and Seybold, 1968). The tumour may infiltrate deeper structures and the corpora cavernosa (Pack *et al.*, 1963).

Microscopic. There is slight variation from case to case and the tumours consist for the most part of interlacing bundles of spindle cells with blunted ends, often arranged in a whorled pattern. The differentiation from benign leiomyoma depends on finding cellular pleomorphism, atypical and large nuclei and frequent mitoses. Infiltration of the deeper tissues, specially corpora cavernosa, may be seen. Multinucleate and bizarre cells, and areas of necrosis and haemorrhage, are frequently present in the more malignant varieties (Pack *et al.*, 1963; Bakken *et al.*, 1968; McKenzie Pratt and Ross, 1969).

Behaviour and Prognosis

McKenzie Pratt and Ross (1969) separated these tumours into 2 groups. The first (Levi, 1930; Kreibig, 1931; Meller, 1932; Ashley and Edwards, 1957) are those arising from the smooth muscle of the superficial tissues of the shaft of the penis. These are of low malignancy, show little tendency to invade deeper structures, and are painless and are not accompanied by urinary symptoms. They tend to recur after local excision. The second group (Fagundes *et al.*, 1962; Pack *et al.*, 1963) arise from the smooth muscle of the corpora. They are situated deeply at the root of the penis in close proximity to the urethra, show local invasion specially of corpora and cause urinary symptoms due to compression of urethra. As the follow-up in all these cases has been short and non-existent in some cases (Levi, 1930; Kreibig, 1931; Meller, 1932), it is not possible to generalise on the behaviour of the tumours. As all the malignant tumours eventually invade the deeper connective tissue and the corpora it is virtually impossible to decide whether the origin was from the smooth muscle of the superficial structures or from the corpora. Certain histological features, such as degree of pleomorphism, presence of bizarre and giant cells, frequency of mitosis, necrosis and invasion of the blood spaces of corpora, may be significant and of help in assessing prognosis. Pack *et al.* (1963) described a case of early multiple secondary deposits in lung from the tumour which had invaded the corpus cavernosum. That the biopsy may not be representative is suggested by the case of Bakken *et al.* (1968) (Table). They graded the biopsy as gr. I, surgical specimen as gr. II or III, and the post-mortem as gr. IV. The authors suggested that the post-mortem specimen represented the change to a more malignant variety, but it was not clear that the surgical specimen did also represent such a change from gr. I to gr. II or III. Metastases are usually blood-borne. No inguinal lymph node involvement has been recorded in any case. The case of Bakken *et al.* (1968), however, showed involvement of the pelvic nodes at post-mortem, and this suggests that the lymphatic dissemination does occur occasionally, but specially in the later stages of the disease. Local recurrence was not the rule, even in those cases where local excision was carried out. In Kreibig's case (1931), a small nodule was excised at the age of 12, further small nodules removed at age 39. No histological studies were carried out. In the case of Ashley and Edwards (1957), a small nodule was removed from the same site, 18 years previously. Again, no histology was done. Because of the lack of histological proof, these cannot be regarded as the true recurrences of the same tumours, especially since their recent histological features are highly pleomorphic, and in Kreibig's case invasion of the corpora is also present. It

Series	Age in Yrs	Site	Gross Description	Histopathological Features	Operation	Radiation	Survival and Recurrence
1. Levi (1930)	38	Dorsum of shaft of penis	Large hard lobulated tumour, freely mobile from underlying structures (A small nodule since childhood.) Increasing for 12 months	Interlacing bundles of spindle cells Many tumour giant cells Frequent mitosis	Local excision	None	No follow-up
2. Kreibig (1931)	46	Dorsum of shaft of penis	Hard plaque 1·5 cm. Local excision. Recurrence of hard grey-white nodules after 8 months	Interlacing bundles of spindle and polygonal cells. Infiltration of connective and vascular spaces of corpora	Total amputation	Given a course without effect before surgery	At age 12, a small nodule removed from prepuce. At age 39, further small nodules removed. Histology of these two unknown
3. Meller (1932)	64	Shaft of penis proximal to coronal sulcus	Mass of 4 cm with firm consistency throughout	Interlacing spindle cells. Giant cells + Infiltration of connective tissue	Total amputation	Radiotherapy given on the clinical diagnosis of angioma—no relief	No follow-up
4. Ashley and Edwards (1957)	67	Shaft of penis proximal to coronal sulcus	Lobulated pinkish-brown tumour with an area of ulcer. Size 2 × 2 × 1·5 cm³ freely mobile	Bands of interlacing spindle cells. Pleomorphism + + Mitosis + +	Local excision	None	Alive and free of recurrence 1½ yrs. after operation. A small nodule at same site removed 18 yrs. ago. No histology done
5. Fagundes *et al.* (1962)	55	Vertical portion at junction of root of penis and scrotum	Size of nut (no dimension) fasciculated whitish mass	Spindle cells mainly with blunt ends. Giant cells + Pleomorphism and atypicality +	Total amputation	None	Alive and free of recurrence for 10 months after operation
6. Pack *et al.*	83	Shaft of penis in right corpora cavernosum	Tan grey fleshy mass, 4 × 3 × 2·5 cm³. Cut surface—cystic and haemorrhagic	Large spindle cells with vesicular nuclei and prominent nucleoli. Pleomorphism + + Foci of necrosis. Blood sinuses infiltrated	Total amputation	Chest secondaries treated by radio-active Yttrium 90	Recurrence of secondaries in chest (X-ray—multiple opacities) 8 months after operation. Response to treat.—good

Series	Age in Yrs	Site	Gross Description	Histopathological Features	Operation	Radiation	Survival and Recurrence
7. Chaudhuri *et al.* (1966)	40	Prepuce glans penis (tip)	Pale pink homogenous mass with ulceration, cut surface—silky with haemorrhage	Interlacing spindle cells with whorls. Pleomorphism + + Giant cells + + Mitosis + +	Total amputation with inguinal block dissection	None	Alive and free of recurrence 3 yrs after operation
8. Bakken *et al.* (1968)	60	Root of penis at junction between anal canal and base of scrotum	Pink, firm mass with areas of haemorrhage	*Biopsy:* spindle cells with some giant cells and (slight) pleomorphism + Grade I *Surgical Specimen:* Spindle cells Pleomorphism + + Giant cells + + Grade II or III *Post-mortem Specimen* Spindle cells Pleomorphism + + + Giant cells + Bizarre cells + + + Necrosis + + Grade IV	Abdomino-perineal resection with suprapubic cystotomy and total penectomy	None	Recurrence in chest 1 month after operation. Died after 6 months with pelvis full of tumour deposits and secondaries in lymph nodes, lungs and liver
9. McKenzie Pratt *et al.* (1969)	38	Root of penis inferior to the urethra	Greyish-white spherical mass 3 cm in diameter and firm consistency	Interlacing bundle of spindle cells. Pleomorphism + + Mitosis + + Giant cells + + Invasion of corpora cavernosa	Total radical amputation of penis with implantation of urethra into perineum	Thiotepa USP (triethylene thiophosphoramide) 30 mg was instilled into the wound	Alive and free of recurrence 2 years after operation
10. Glucker *et al.* (1972)	6	Dorsum of glans penis	Bluish-black lump—1 cm in diameter	Interlacing bundles of spindle cells. Pleomorphism + Mitosis + +	Local excision	None	Alive and free of recurrence 1 year after operation
11. Present study	84	Postero-lateral region of glans penis at the coronal sulcus	Ulcerated, raised homogenous whitish mass, 1·5 × 1 × 1 cm^3. Prepuce adherent	Interlacing bundles and whorls of spindle cells. Mitosis + Pleomorphism + Giant cells none. Necrosis none. No invasion of corpora	Partial amputation	None	Alive and free of recurrence for 6 months

is possible that these previous small nodular lesions are simple locally recurring leiomyoma, possibly incompletely excised. On the same grounds, the present type of case with moderate pleomorphism and mitosis, lack of giant bizarre cells and necrosis, and non-invasion of corpora, should be regarded as of low-grade malignancy and therefore with a relatively better prognosis.

Summary

A case of low-grade leiomyosarcoma of the penis is described. The patient was treated by partial amputation, and is alive and free of recurrence for 6 months.

Ten other previous cases are reviewed and discussed.

I wish to offer my sincere thanks to Dr A. E. Chaplin, Director of Pathology Division, Dudley Road Hospital, for valuable suggestions and help, to Dr W. R. Shortland-Webb and Miss Jean McCulloch for help in photography, and to Miss Vivian Barlow for preparing the text.

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(The following references were all quoted by Ashley and Edwards, 1957: Levi, 1930; Kreibig, 1931; Meller, 1932.)

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Sarcoidosis of the Penis treated by Radiotherapy

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Sarcoid granulomata of the penis are uncommon, only 3 cases having been reported in the literature. In 2 of these sarcoid nodules were present in the skin of the penile shaft (Longcope 1941, and Longcope and Fisher, 1942), and more recently a case has been reported of sarcoid of the skin of the glans penis (Vitenson and Wilson, 1972). All 3 cases occurred in negroes and all had proven systemic sarcoidosis. We report here a case of sarcoidosis of the penis in a white man, the difficulties encountered in treatment and a successful outcome following the use of radiotherapy.

Case History

A Welsh laboratory technician, aged 59, presented in May 1971, with a short history of blood-stained urethral discharge. He also complained of mild pain at the external urethral meatus on micturition, but he had no other urinary or general symptoms.

The only relevant information from his past history was the removal 8 years previously of an enlarged submandibular lymph-node showing a typical sarcoid granuloma (Fig. 1). He received no further treatment and remained well. In 1967 a transurethral resection of the prostate was performed for benign hyperplasia. Following this he developed bladder-neck stenosis which was treated by further transurethral resection.

When he presented in May 1971, examination revealed no abnormality apart from phimosis. When he was examined under anaesthesia, irregular ulcerated tissue was found around the external urethral meatus. Biopsy of this tissue showed a non-specific granuloma (Fig. 2). During the subsequent 8 weeks the ulcerated area increased in extent and the patient was circumcised and a further biopsy taken. Cysto-urethroscopy at this time showed no evidence of any similar lesion higher up in the urethra or in the bladder. The appearance of the penile lesion at

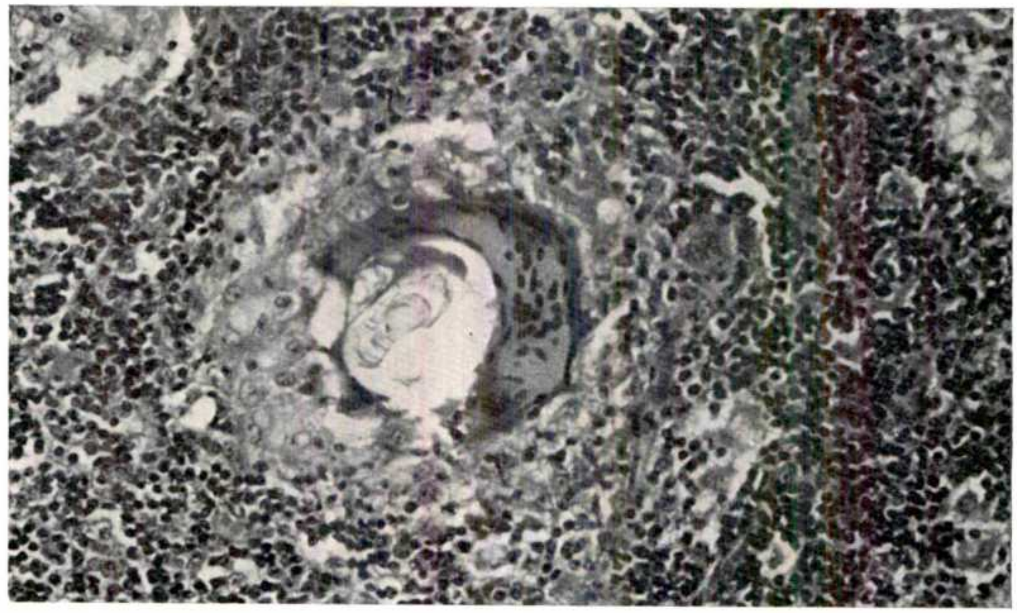


Fig. 1. Lymph node biopsy 1963. The normal lymph node architecture is replaced by sarcoid granulation tissue with giant cells containing Schaumann bodies. H & E. × 40.

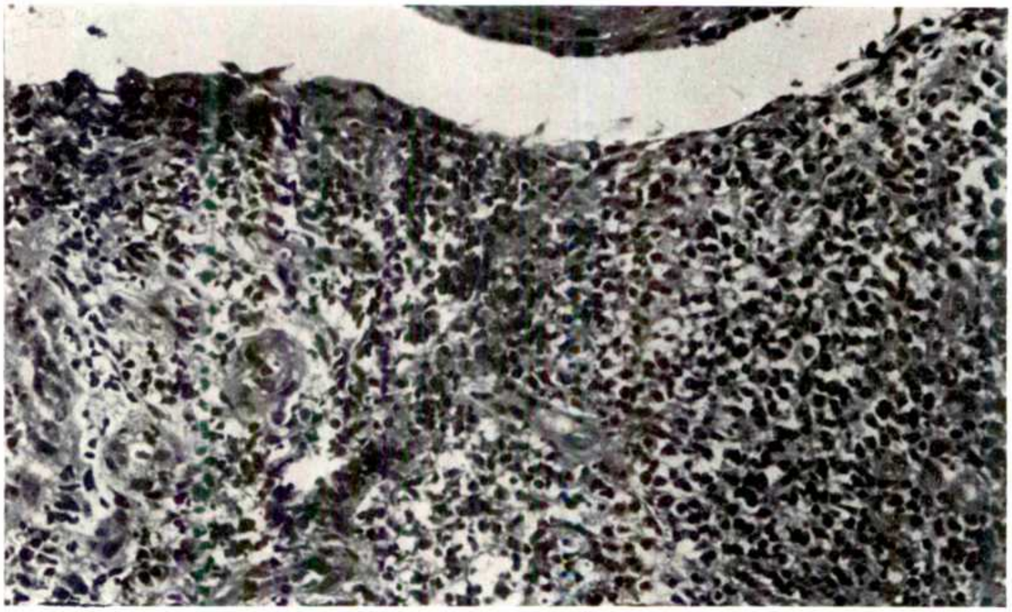
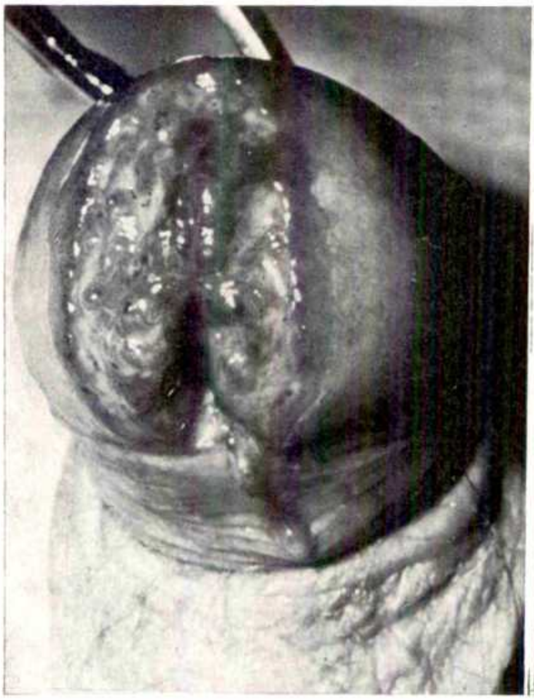


Fig. 2. The first penile biopsy. There is ulceration of the squamous epithelium at one edge. Beneath this is a broad zone of acute and chronically inflamed granulation tissue. H & E. ×40.



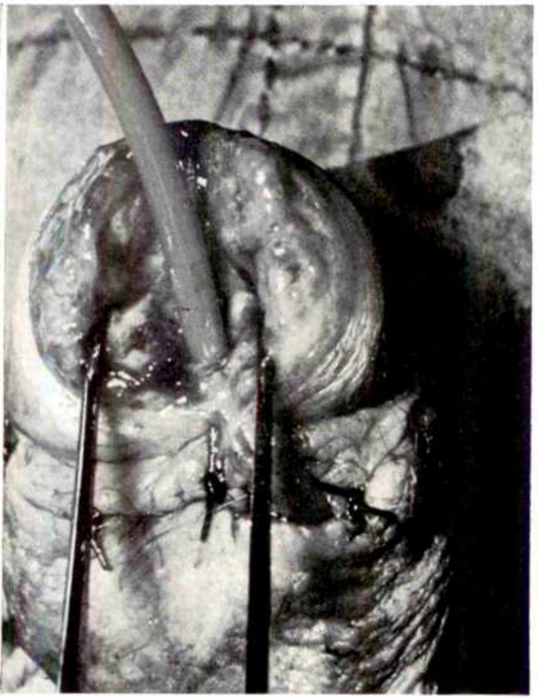


Fig. 3A. The ulcerated area around the external urethral meatus at the time of the second penile biopsy.

Fig. 3B. The granuloma is seen to extend up the urethra which is marked by the catheter.

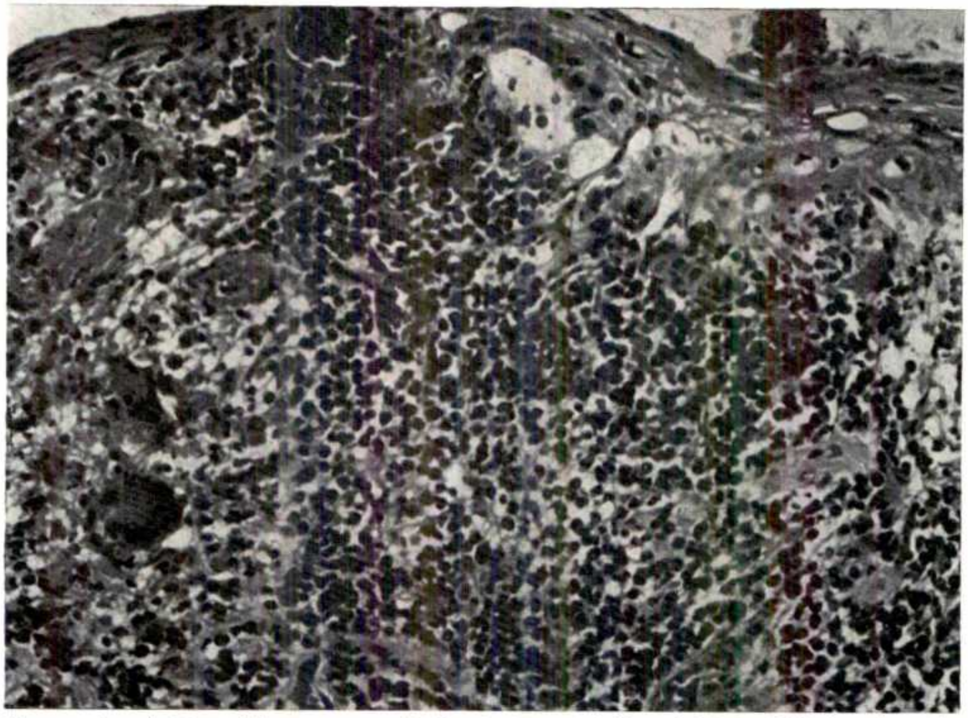


Fig. 4. The second penile biopsy. The squamous epithelium is attenuated. Beneath this is a follicular, giant-cell granulomatous reaction of the sarcoid type. H & E. × 40.

this time is shown in Figure 3A and 3B. The biopsy was reported as follicular non-caseating granuloma with giant-cells consistent with a diagnosis of sarcoid (Fig. 4). A skin lesion of the anterior chest wall was excised and this showed a similar histological picture.

Investigations

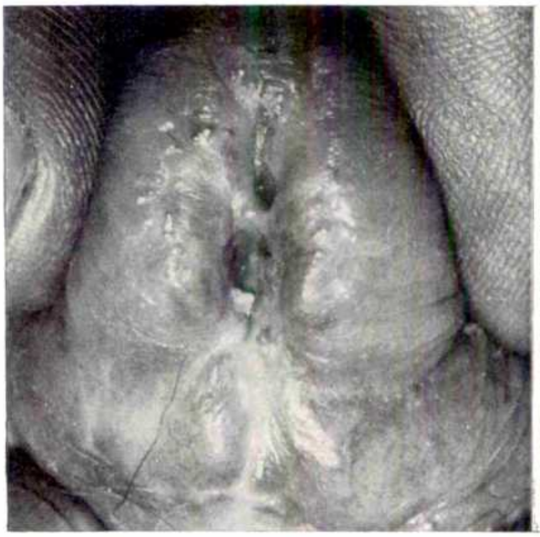
The haemoglobin and white blood count were normal. The sedimentation-rate was raised at 55 mm in the first hour. Serum electrolytes, proteins, calcium and phosphate were all within normal limits. The Wassermann reaction, the GCFT and the VDRL test were negative. The Mantoux test was weakly positive at 1: 1,000. Intensive bacterial and viral studies on the biopsied material all showed no evidence of infection. Chest radiography revealed no abnormality. A Kveim test was not carried out at this stage because of the urgent need to treat the patient. The test was carried out later and was negative but the reaction may have been suppressed by the steroid therapy that the patient was by then receiving.

Treatment and clinical progress

Prednisone 30 mg daily in divided doses was given for the first month and the dose was then reduced to prednisone 20 mg daily. The ulcerated area around the external urethral meatus healed within 2 months (Fig. 5), but as it healed a meatal stricture developed for which a meatoplasty was performed in October 1971.

The patient remained on steroids and in good health until May 1972, when he began to complain of pain in the glans penis and soreness at the meatus. He also had severe side-effects from his steroid therapy. On examination there was tenderness and induration of the glans penis and scabbing at the meatus, and by the end of June 1972, two further areas of ulceration of the glans penis had developed (Fig. 6). In July 1972, a partial amputation of the penis was performed in an attempt to eradicate the disease and to obviate the need for further steroid therapy. Histological examination of the excised specimen showed chronic abscess formation deep within the glans penis. His recovery from this procedure was uneventful but one month later he again noticed intermittent bleeding. He was found to have developed an ulcer at the cut ends of the corpora cavernosa (Fig. 7). This was biopsied and histological examination showed a prominent chronic inflammatory cell infiltrate which was chiefly lymphocytic. Although no follicles were seen the appearances were disturbingly like those of the original biopsy (Fig. 8).

The patient was transferred to Cookridge Hospital for high energy irradiation, and was given 15 treatments in 19 days, a maximum dose of 3,200 rads being given to the penile stump. There was an immediate and dramatic



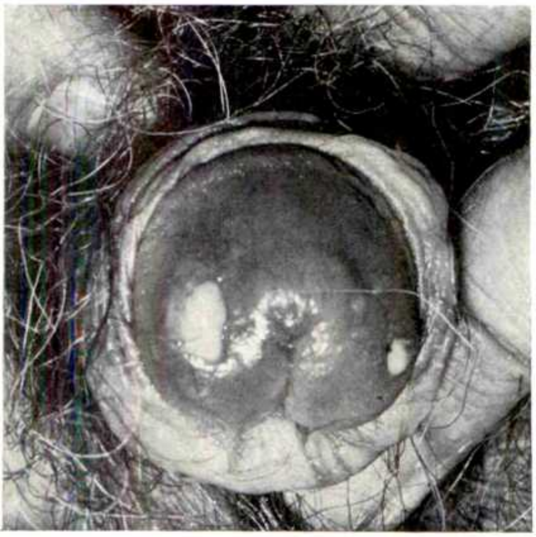


Fig. 5. The initial response to steroid therapy. The ulceration around the meatus has healed.
Fig. 6. Two further areas of ulceration which developed during steroid therapy.

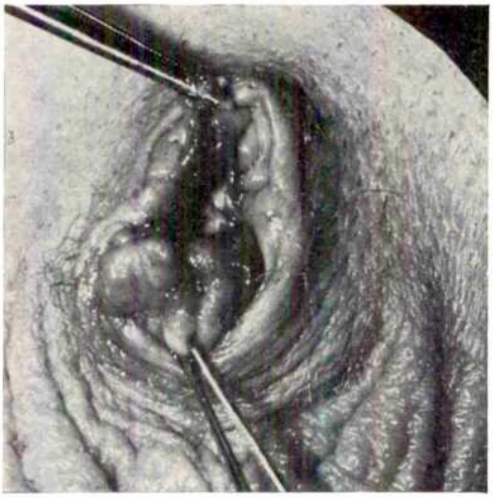


Fig. 7. Ulceration at the cut ends of the corpora cavernosa after partial amputation of the penis.

improvement in the lesion during this treatment and the ulcerated area healed. It has remained healed and the appearances 1 year later are shown in Figure 9. Steroids were gradually withdrawn and stopped 3 months after radiotherapy was completed. Unfortunately, the patient developed severe osteoporosis of the dorsal spine and has to wear a spinal support. He is now receiving calcium supplements and Vitamin D.

When the patient was reviewed in October 1973, he was well and was having no difficulty with micturition. His penile stump was well healed, his meatus was of good calibre, and his urinary flow-rate was normal (20 ml/sec).

Discussion

The present case emphasises a number of interesting points. An ulcerating sarcoid granuloma of the penis has not previously been described. As can be appreciated from the illustrations, the initial lesion had so many of the features of a carcinoma that two separate biopsies were performed.

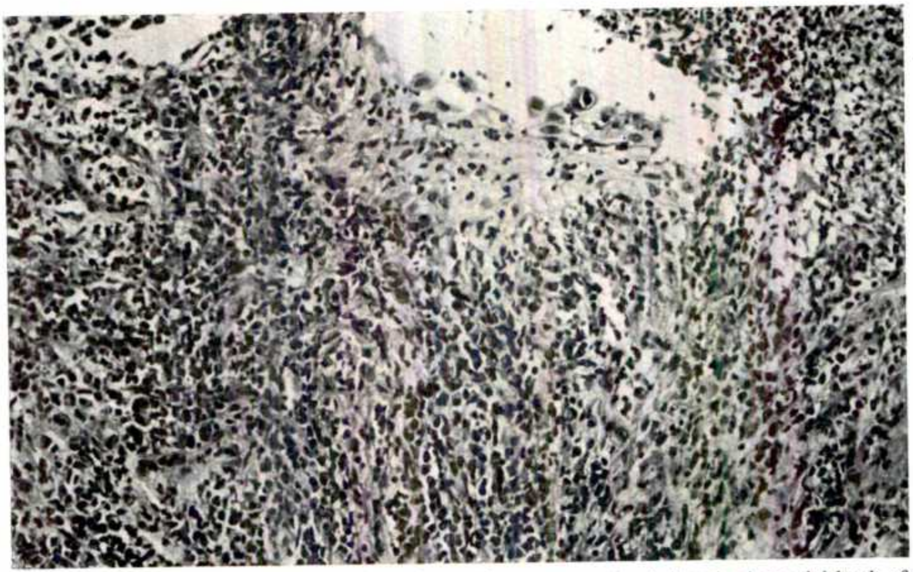


Fig. 8. Biopsy of the amputation stump. There is a chronic granulomatous reaction infiltrating beneath islands of epidermis. The appearances resemble the first biopsy closely. H & E. ×40.

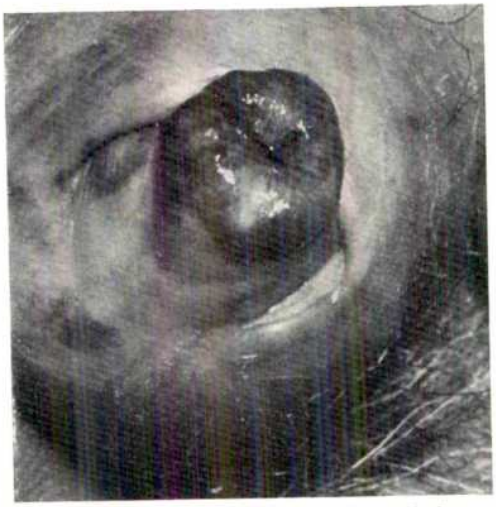


Fig. 9. The amputation stump healed after radiotherapy.

The site of the initial lesion might suggest that the local trauma during transurethral resection may have been a factor in the causation of the lesion. Against this hypothesis is the long time interval, 4 years, between the second instrumentation and the development of the lesion. The multiple lesions of the skin and the previous involvement of the submandibular lymph node provide good evidence to support the diagnosis of systemic sarcoidosis.

In spite of the good initial response of the lesion to treatment with steroids, the lesion reasserted itself while the patient was still taking moderately high doses of prednisone. The recurrent ulceration and the abscess formation deep within the substance of the glans penis were no longer related to the urethra, as had been the case with the meatal lesion. When the granuloma recurred after the partial amputation of the penis, the recurrence was in the corpora cavernosa.

Radiotherapy is generally considered to be ineffective in the treatment of sarcoid lesions. Bernstein and Oppenheimer (1942) reported encouraging results in 4 cases, but of Donlan's 11 cases only 1 showed any improvement (Donlan, 1948). Her patients were treated with a 200 kV. apparatus and were given an average dose of 1,500-2,000 rads. The only lesions that responded had been given 2,500-3,000 rads. We can find no reports in the literature of the effects of high energy irradiation on sarcoid lesions. In one of Bernstein and Oppenheimer's patients a large mass of cervical lymph-nodes disappeared in 2 weeks following radiotherapy. An equally gratifying result was seen in the present patient.

Our patient will be kept under review and a further report made if the disease recurs locally.

Summary

A case of sarcoidosis of the penis is reported which initially caused ulceration around the external urethral meatus.

After an immediate response to steroid therapy, the disease recurred locally in spite of continuing therapy and involved other parts of the penis.

Partial amputation of the penis was performed but further ulceration occurred at the cut ends of the corpora cavernosa in the penile stump. This ulceration healed after radiotherapy.

We wish to thank Professor B. E. C. Nordin, Dr N. G. Rowell and Dr H. G. Frank for their help in the management of this patient. We also wish to thank the Department of Medical Photography for the illustrations.

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Idiopathic Fat Necrosis in the Scrotum

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The clinical differential diagnosis of scrotal pain and a scrotal mass in the prepubertal male is often perplexing. The entities of torsion, orchitis, epididymitis and epididymo-orchitis often offer very few signs of diagnostic certainty and the frequency of error in diagnosis—especially in cases of torsion—is well known.

The policy at the Christchurch Hospital is to explore all acute scrotal swellings in all patients under 18 years of age regardless of the preoperative diagnosis.

Recently 2 young males presented to the Christchurch Hospital with a very unusual entity which must enter into the differential diagnosis. The 2 cases are described.

Case 1. An 11-year-old white male presented on 21st October 1971 with bilateral scrotal aching and reddening. He denied all other urological and constitutional signs and symptoms. There was no past history of cryptorchidism, retractile testes, allergy or trauma. On physical examination he was well developed, well nourished, not obese; temperature 98·6°, pulse 84. The penis was circumcised and normal, and his urethra was normal. His scrotal wall was reddened, not oedematous and of normal temperature. Both testes were palpable high in the neck of the scrotum. There were asymmetrical scrotal masses below the testes (Fig. 1). The right mass measured 3 cm by 1 cm by 1 cm; it was hard but not tender; it was neither hot nor pulsatile. The left mass measured 1 cm by 1 cm by 1 cm; although firm it was neither tender nor hot. A diagnosis of testicular torsion could not be excluded.

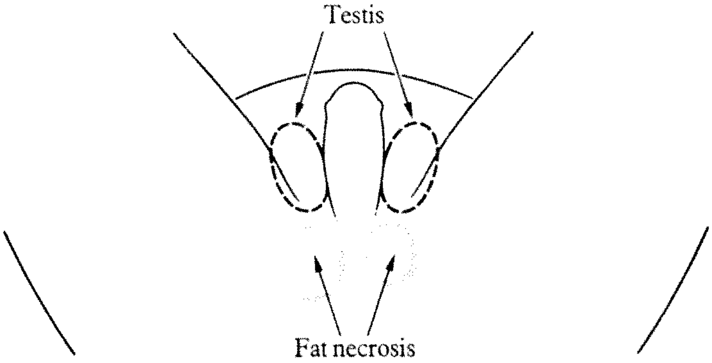

Fig. 1. View of scrotum showing high location of the testes and the bilateral asymmetrical masses of necrotic, inflamed fat beneath them.

Full blood count, urinalysis, urine culture were normal. Eosinophil count was normal. With the diagnosis in doubt, the right scrotal sac was explored through a transverse incision. The tunica vaginalis was intact and the testis located within it. The mass rose from the base of the tunica vaginalis in the area of the gubernaculum and the mass was excised. It was easily separable. It appeared bright yellow in colour and was sent for histological examination. The other side was not explored.

The pathological report was as follows:

A piece of firm fat, 3 cm by 2 cm by 1 cm.

Histological examination (Fig. 2, A and B) showed an inflammatory infiltrate of lymphocytes, eosinophils, plasma cells and histiocytes in the fat, and fibrous trabeculae with small areas of organising fat necrosis.

Case 2. An 11-year-old white boy in excellent health was admitted to hospital with the complaint of bilateral scrotal pain and oedema of the scrotum of 2 days' duration. There were no other urological or constitutional complaints. There was no history of cryptorchidism, retractile testes, trauma and no allergic history. The remainder of the past history was non-significant. On physical examination he was well developed, well nourished, not obese

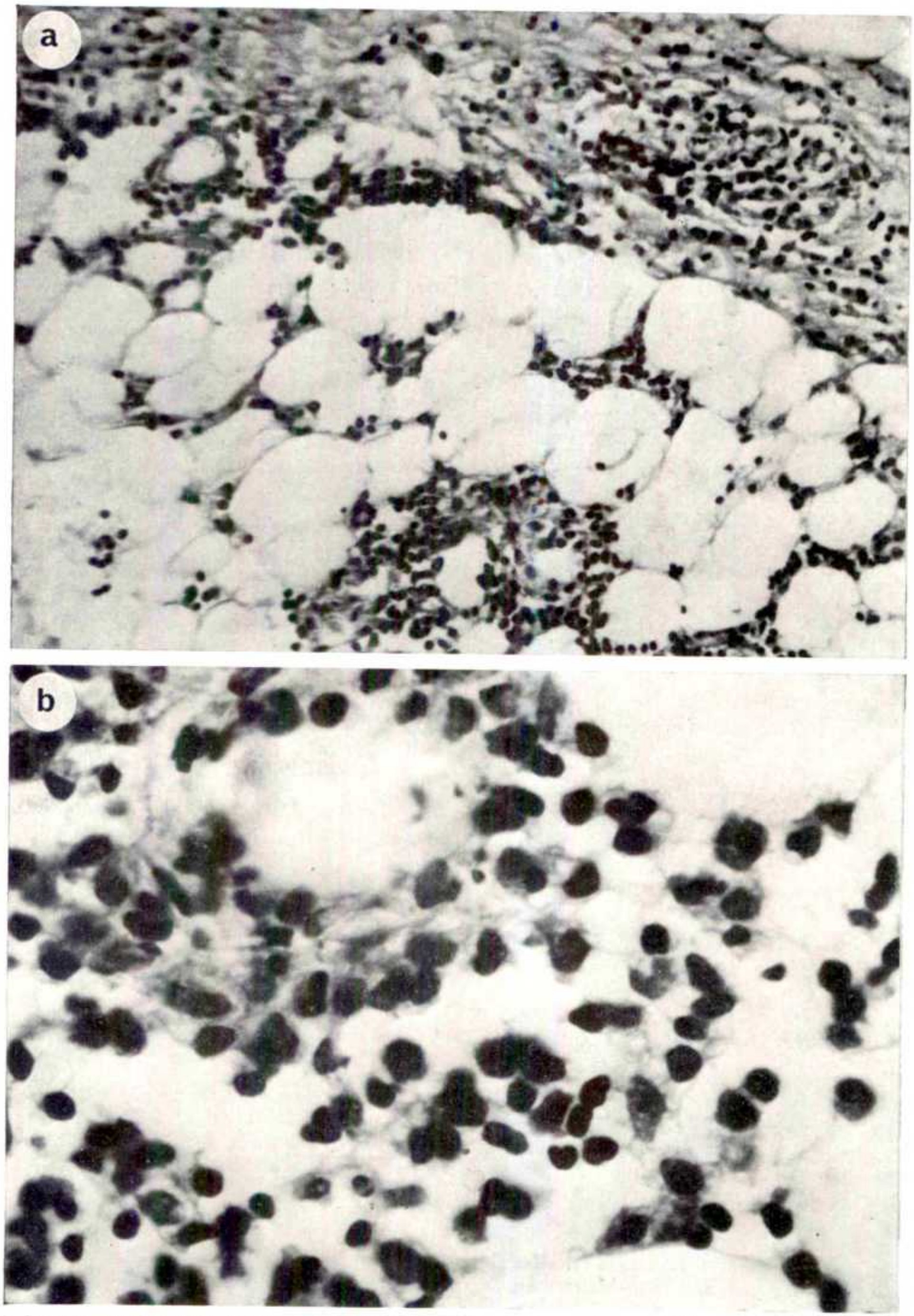

Fig. 2. A, Low power view of fat mass. ×175. **B**, High-power view of mass showing inflammation, infiltration and small areas of organising fat necrosis. ×700.

and in no acute distress. The temperature was 98·6°, pulse 84 and regular. On physical examination of the abdomen and external genitalia, there were no signs of puberty. The penis was circumcised and normal. The urethra was normal. The scrotum was reddened, not oedematous nor hot. Both testes were palpable in the scrotal neck. The scrotum had symmetrical scrotal masses 1 cm by 1 cm by 1 cm, hard, non-tender, not hot and non-pulsatile. Elevation of the masses on both sides did not alleviate the aching.

Apart from some eosinophilia a full blood count, urinalysis and urine culture were normal.

A diagnosis of idiopathic fat necrosis was made and the patient was treated conservatively.

Discussion

In 1939, Hinman described 3 cases of a new entity, fat necrosis in the scrotum, and concluded that it occurred in stout young men before puberty with normally placed testes. The necrosis was acute in onset, accompanied by pain and tenderness but no other findings except for the mass which could not be recognised as being separate from the testis. Microscopically, fat necrosis and an inflammatory reaction in the fatty tissue were noted. He described the 3 boys, aged 10, 12 and 11, 2 of whom were rather stout and suffered from this after cycling. The third was returning from swimming.

Macbeth and Douglas in 1968 presented 2 additional cases in obese prepubertal males with antecedent histories of swimming in cold ocean water. His boys were aged 9 and 11. Macbeth classified the entity as occurring in the scrotum of individuals with a minor history of trauma, the masses being bilateral and symmetrical, being located posterior and inferior to the testis and being unassociated with any systemic disturbance.

Grugni in 1954 described for the first time the presence of lipomatous tissue in the scrotum in the prepubertal male. The adult male scrotum anatomically does not contain fat. In Macbeth's cases, swimming was incriminated. Both of our cases had been in the ocean swimming 5 days prior to admission to the hospital and 3 days prior to the onset of pain. At that time, off Christchurch, the temperature of the ocean water was 55°F. The combined aetiology of trauma, cold and salt water acting on the scrotal fat resulting in idiopathic fat necrosis is proposed.

Conservative treatment can be carried out when the diagnosis can be made with confidence. In this particular entity the presence of the testes high in the scrotal neck must be searched for and then the diagnosis established.

On follow-up 6 weeks later, the first boy who had been explored no longer had any scrotal mass present on the opposite side and the other boy who had been treated conservatively was also free from pain and abnormal scrotal masses.

Summary

2 cases of idiopathic scrotal fat necrosis are presented.

The aetiology and differential diagnosis are discussed.

Trauma, cool temperature and ocean water all appeared to be relevant factors in its production.

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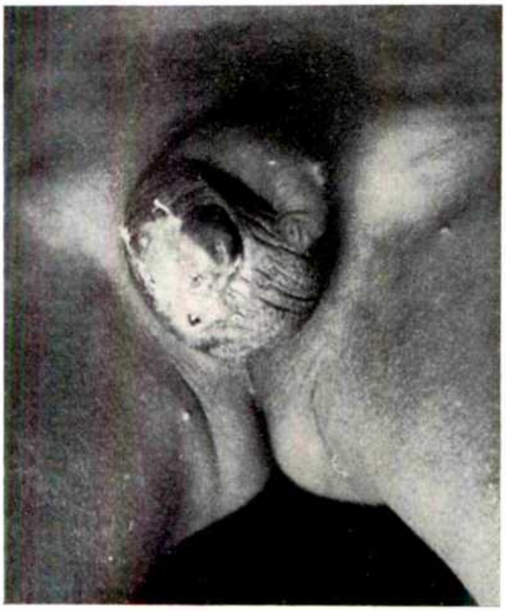
Short Case Report

Scrotal Skin Necrosis following Snake Bite

An Adivasi boy aged 5, with local necrosis of the right side of the scrotal skin, was admitted with a history of being bitten by a snake on his scrotum 3 days previously. The snake first entangled his feet while playing in a paddy field and when he tried to throw it off, he was bitten. The snake was killed by people who witnessed the scene. He was treated by witchcraft and a quack. The boy developed fever with red painful swelling of the scrotum within 12 hours, and ulceration of the scrotal skin after 2 days (see Figure). There was no history of any irritant application. By daily dressing and parenteral antibiotics, the wound healed gradually. Tetanus Toxoid was also given. The testis and cords were normal clinically.



Comments

The interesting feature of this case was the rare site of the snake bite, which resulted in local necrosis with no systemic manifestations (neurotoxic or haemorrhagic). Most probably, the snake was non-poisonous; if it was poisonous, either the toxin was not injected at all or the dose was sublethal and sufficient only to cause local necrosis.

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Ampicillin, Carbenicillin Indanyl Ester, and Nifuratel in the Treatment of Urinary Infection in Domiciliary Practice

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There are a number of reports of the successful use of parenteral carbenicillin in the treatment of urinary infections but controlled trials with this antibiotic are lacking (Davis, Iannetta and Wedgwood, 1971), and it is only minimally absorbed when taken by mouth. The newly introduced indanyl ester of carbenicillin is absorbed when given orally, being rapidly hydrolysed to yield free carbenicillin which is subsequently excreted in the urine in high concentration. For the oral therapy of urinary infection nitrofurantoin is well established, although the recommended dose produces nausea in a substantial number of patients. Another nitrofuran, nifuratel, presented in a 200 mg sugar-coated tablet, has been studied and preliminary reports suggest that it is as effective as nitrofurantoin but causes fewer side-effects. During the planning of the present trial a 400 mg non-sugar-coated nifuratel tablet became available and because of the possibility that the kinetics of absorption might be different (thus influencing the gastrointestinal side-effects as well as altering the therapeutic efficacy of the compound) it was decided to include both nifuratel preparations in the treatment trial.

Since experience with the new preparation of carbenicillin is limited and nifuratel has rarely been used in the treatment of urinary infections (Tynan, Macis and Ward-McQuaid, 1969; Brumfitt, 1972), comparison with a drug of predictable efficacy seemed essential. For this reason, ampicillin, a well established drug in the oral treatment of urinary infection, was selected. Thus it was considered worthwhile to compare ampicillin, carbenicillin indanyl ester and the 2 nifuratel preparations in a double-blind treatment trial in 2 different defined groups of domiciliary patients.

The Patients

Altogether, 120 patients were divided into 2 separate groups, the first being 65 non-pregnant females and 2 males who were referred by their general practitioners to the urinary infection clinic because of dysuria and frequency. These patients had received at least one course of chemotherapy from their own doctors, with unsatisfactory results, and 48 of them (72%) were still symptomatic when first seen at the clinic. The second group consisted of 53 patients referred from the antenatal screening clinic with bacteriuria in pregnancy. Many of them had suffered urinary infections in previous pregnancies and 26 (49%) had urinary symptoms at the first clinic attendance.

The Organisation of the Trial

After each patient was shown to fulfil the criteria for inclusion in the trial (see laboratory methods), a 7-day supply of the allocated drug was given. The dosage employed was 500 mg 6-hourly for ampicillin and carbenicillin indanyl ester, and 400 mg 8-hourly for the 2 nifuratel preparations. The 4 treatments were allocated according to a random number list by a person unconnected with the trial, and those patients who failed treatment were given 1 of the 3 remaining compounds. Thus 67 non-pregnant patients received 91 courses of treatment, and 53 women with bacteriuria in pregnancy received 72 courses of treatment. At each visit, a proforma was completed and the patients were asked in a general way for their opinions on the treatment just received. After this, they were questioned directly concerning the disappearance of symptoms as well as any side-effects of the drug used. Blood samples were obtained at every visit throughout the study for haematological, biochemical and immunological assessment of the patient's response to infection and to assist in the evaluation of possible side-effects of chemotherapy.

The sole criterion of cure was the eradication of the original infecting organism from the urine at 2 and 6 weeks after the beginning of treatment. The treatment was considered to have failed if the same organism, as judged by its biochemical and serological characteristics, was isolated from either of the follow-up specimens. In some cases this meant that the immediate post-treatment urine was clear, but the specimen taken approximately 6 weeks after the beginning of treatment yielded a significant growth of the original organism. Treatment was considered to be successful even if the urine, either at 2 or 6 weeks, yielded a significant growth of a *different* organism since this must be due to reinfection. Such reinfections were found after 18% of courses in the non-pregnant patients, and after 11% of courses in the pregnant women. When patients had repeated urinary infections despite adequate treatment, intravenous pyelography was carried out to exclude the presence of abnormalities.

The non-pregnant patients who responded to treatment were followed up for at least 6 weeks before being referred back to their general practitioners, and the pregnant women were seen at intervals up to 6 weeks after delivery.

Laboratory Methods

The criterion for inclusion in the treatment trial was that 2 successive mid-stream specimens of urine collected at the clinic were shown to contain more than 10^5 organisms per ml of the same bacteria in pure growth. Mid-stream specimens of urine were collected from the patient after swabbing with sterile water. Antiseptic agents were not used in perineal preparation since it has been shown that they may interfere with bacterial cultures (Roberts, Robinson and Beard, 1967). These mid-stream specimens were tested for protein and glucose, and urinary cell counts were carried out in a modified Fuchs-Rosenthal chamber. Semiquantitative bacterial counts were performed using the blotting paper strip technique (Leigh and Williams, 1964) and those positive by this test were cultured quantitatively by a surface spread plate dilution method. The organisms were identified by standard methods (Cowan and Steel, 1965) and antisera were used to determine the serotype of each *Escherichia coli* isolate. Serum antibody titres against the urinary organisms were estimated by the method of Percival, Brumfitt and de Louvois (1964).

Results

Table I lists the causal organisms in the 2 groups of patients, and analysis of these figures reveals that there is a significant difference in the prevalence of staphylococcal infection in the 2 groups (Fischer exact test, $P = 0{\cdot}03$). There are no significant differences, however, between the figures for *Esch. coli* or *Proteus mirabilis*. The *Esch. coli* serotypes responsible for the infections in both groups of patients were very similar to those described by most other workers (for example, Grüneberg, Leigh and Brumfitt, 1968), with serotypes 06 and 075 predominating in the non-pregnant patients, and 02 and 075 serotypes in the pregnant women with bacteriuria.

Non-Pregnant Patients

The 67 patients in this group received 67 primary, 20 secondary and 4 tertiary courses of treatment. Table II shows that the nifuratel compounds were marginally more effective than ampicillin,

Table I

Infecting Organisms in the 2 Groups of Patients*

Causal Organisms	Non-Pregnant Patients	Pregnant Patients
Escherichia coli	67 (85%)	49 (79%)
Staphylococcus albus	8 (10%)	1
Proteus mirabilis	4 (5%)	6 (10%)
Klebsiella aerogenes	...	4
Streptococcus faecalis	...	2

* *Note:* Some patients had more than one infection whereas others were treated twice or more for the same infection.

Table II

Results of Treatment in Non-Pregnant Patients

	Courses		
Drug	Total	Success (%)	Failure
Ampicillin	22	17 (77%)	5
Carbenicillin ester	25	18 (72%)	7
Nifuratel 200 × 2 coated	19	16 (84%)	3
Nifuratel 400 × 1 uncoated	25	22 (88%)	3
	91	73 (80%)	18

$\chi^2 = 2{\cdot}32$, P = 0·5 = Not significant

and considerably more effective than the carbenicillin indanyl ester: however, when these figures are examined in more detail the differences are much reduced. There were fewer secondary treatment courses with the sugar-coated nifuratel: if the primary courses only are considered, the success percentages are as follows: ampicillin 88%, carbenicillin ester 76%, coated nifuratel 80%, and uncoated nifuratel 89%. Thus the removal of the secondary courses makes little difference to the results with carbenicillin and the nifuratel compounds, but much improves the results with ampicillin. Analysis of the failures of secondary treatment reveals that they all occurred where the infection was recalcitrant to at least 3 different antimicrobial agents. These patients were referred for full urological investigation.

Patients with Bacteriuria in Pregnancy

A total of 53 patients received 72 courses of treatment, of which 53 (74%) were successful (Table III). The large number of treatment courses is due to the fact that relapse or reinfection occurred in some patients necessitating an additional course of treatment.

Combined Results (All Patients)

The overall results of 163 courses of treatment given to 120 patients are shown in Table IV. It should be noted that combining the results from 2 separate groups of patients disguises the differences found when an individual group, pregnant or non-pregnant, is considered alone. Results of both the primary and total treatment courses showed no statistically significant differences

Table III

Results in Patients With Bacteriuria in Pregnancy

Drug	Courses		
	Total	Success (%)	Failure
Ampicillin	19	13 (68%)	6
Carbenicillin ester	18	14 (77%)	4
Nifuratel 200 × 2 coated	17	11 (65%)	6
Nifuratel 400 × 1 uncoated	18	15 (83%)	3
	72	53 (74%)	19

$\chi^2 = 1{\cdot}99$, P = 0·5 = Not significant

Table IV

Combined Results in the 2 Groups of Patients

Drug	Total Treatment Courses	
	Given	Success (%)
Ampicillin	41	30 (73%)
Carbenicillin ester	43	32 (74%)
Nifuratel—coated	36	27 (75%)
Nifuratel—uncoated	43	37 (86%)
Totals:	163	126 (77%)

between the 4 drug preparations, although the uncoated nifuratel appeared to be marginally superior. A possible explanation for some of the failures with carbenicillin may be the number of unwanted side-effects observed by the patients and the possibility that some treatment courses were not completed.

Unwanted Effects

The frequency of side-effects was significantly greater ($\chi^2 = 6{\cdot}75$, P = 0·01) with the 2 penicillins, considered either separately or together, than with the nifuratel compounds (Table V). There was no significant difference between the penicillins themselves ($\chi^2 = 0{\cdot}43$, P = 0·5) in the number of side-effects encountered.

A number of patients complained of gastrointestinal disturbances (mainly nausea and vomiting) which occurred with all 3 drugs used. They often complained that carbenicillin tablets were difficult to swallow and gave rise to an unpleasant taste sensation, usually described as a "medical" taste. The reason for the side-effects with the carbenicillin ester may be that the tablets consisted of 500 mg of the compressed carbenicillin preparation, and were brick-shaped with sharp edges: no surface coating was provided. Since the present study was concluded, the manufacturers have produced a film-coated 500 mg tablet of smaller size with a smooth surface (Knirsch, Hobbs and Korst, 1973) and a further trial of the new preparation is in progress. Eight of the patients who received ampicillin suffered from diarrhoea of varying degree. Remarkably few side-effects, seldom amounting to more than mild nausea and flatulence, were noted after treatment with either of the nifuratel preparations. Only 1 patient complained of a skin eruption, which was acneiform and apparently related to the administration of carbenicillin. None of the 41 patients who received ampicillin developed a rash. Six patients suffered from oral or vaginal thrush (from which *Candida albicans* was isolated), 3 following ampicillin and 3 after carbenicillin. Mucosal

Table V

Frequency of Unwanted Drug-Effects

Drug	Courses Given	Courses with Side-Effects (%)
Ampicillin	41	13 (32%)
Carbenicillin ester	43	18 (42%)
Nifuratel—coated	36	5 (14%)
Nifuratel—uncoated	43	6 (14%)

Table VI

Side-Effects Noted During Therapy*

Drug Given	Ampicillin	Carbenicillin Ester	Nifuratel Coated	Nifuratel Uncoated
Number of Courses	41	43	36	43
Complaints Noted:				
Unpleasant/difficult to swallow	...	11	...	...
Vomiting/nausea/flatulence	...	4	3	3
Diarrhoea	8	2	1	...
Oral/vaginal candidiasis	3	3	...	...
Miscellaneous	4	2	1	4
Totals:	19	22	5	7

* *Note:* Some patients had more than one side-effect during the same course of treatment.

irritation was not found in any patient who received nifuratel. The side-effects noted are recorded in Table VI. The unwanted effects were severe enough to curtail treatment in 3 patients on carbenicillin therapy: all had difficulty in swallowing the tablets and 1 of them also experienced severe diarrhoea. One of the patients given ampicillin reported vaginal and oral thrush as well as severe diarrhoea and discontinued her medication.

Discussion

As can be seen from the results, there was little difference between the effectiveness of the antibacterial compounds used. The carbenicillin ester was satisfactory in treatment but had the disadvantage of being rather poorly tolerated by the patients. The latter finding is in agreement with Bailey and Koutsaimanis (1972) and Turck (1973). With improved formulation now available, this drug should have a place in the treatment of *Pseudomonas aeruginosa* urinary tract infections, particularly in ambulant out-patients (*British Medical Journal*, 1973). However, in the present study no *Ps. aeruginosa* infections were encountered.

When the results of treatment were related to the bacteria isolated, it was found that the majority of the staphylococcal infections (8 out of the 9) were treated with the nifuratel compounds. Our experience in treating such infections is that they almost always respond to chemotherapy within 24 hours; this was also seen in the present study. Thirteen treatment courses were given for *Proteus mirabilis* infection, of which 6 were with the carbenicillin ester and 4 were successful. The nifuratel compounds were used in 4 episodes of infection due to this organism, and were successful in 3 instances. This is surprising since nitrofurantoin, another nitrofuran, generally fails to cure proteus infections. The 3 remaining infections due to the organism were all in pregnant women and were treated with ampicillin but only 1 was cured. None of the strains of *P. mirabilis* produced penicillinase.

In order to assess the value of the different treatment regimes in the presence of renal tissue involvement, the patients were divided into 2 groups according to the presence, or absence, of a raised titre of bacterial agglutinins in the serum (Percival, Brumfitt and de Louvois, 1964). The results showed that there were no statistically significant differences between the cure rates in the 2 groups of patients. However, it is clear that both nifuratel preparations were effective in patients who had renal tissue infection accompanied by raised serum antibody titres and this has been borne out by the successful use of these drug preparations in patients with acute pyelonephritis. It has been shown that although the nitrofurans reach negligible concentrations in the blood they are capable of diffusing into the medulla of the kidney (Chisholm, Calnan and Waterworth, 1968).

The reversal of the percentage cure rates in pregnant women compared with non-pregnant patients has previously been reported with cephalexin and ampicillin (Brumfitt and Pursell, 1972). In the present study a similar reversal was observed with carbenicillin and ampicillin, suggesting that the lower cure rates with ampicillin in pregnant patients may be evidence of less complete intestinal absorption. As the pregnant women were followed for at least 6 weeks after delivery it was possible to study any teratogenic effects caused by the drugs in the trial. Only in 2 patients (both of whom received carbenicillin and then ampicillin) did foetal morbidity occur. In 1 of them a twin pregnancy aborted at 26 weeks following the development of acute hydramnios and the other, a patient with intractable *Proteus mirabilis* infection and a renal stone, gave birth to an infant with congenital heart disease which proved fatal. The mean birth weights of the infants born to patients in the 4 treatment groups were 7·1, 6·9, 6·8 and 7·1 pounds.

The 2 nifuratel preparations were similar in activity, though there appeared to be a clear advantage in using the uncoated compound, and this drug was particularly effective in bacteriuria in pregnancy. The small number of side-effects was very gratifying, confirming the earlier studies of Brumfitt (1972) in a pilot trial. There were worthwhile additional benefits from its prophylaxis against *Trichomonas vaginalis* and *Candida albicans* (Murphy, 1968; Struthers, 1969; Munro, 1973) although the action against *Trichomonas vaginalis* may be less than that of metronidazole (Fowler and Hussain, 1968; Evans and Catterall, 1970). The cost of these preparations is similar to that of ampicillin.

In view of the findings of minimal antibacterial activity of nifuratel in the urine of volunteers (McGeachie, Robinson and Black, 1972), it is surprising to find such high cure rates following treatment with this drug. Because of this, it is even more surprising that the cure rates were also high in patients with parenchymatous renal infection (judged by raised serum agglutinin titres).

A number of side-effects were seen following the ampicillin courses although the severity was sufficient to stop treatment in only 1 case. By contrast, 3 patients given carbenicillin had to abandon their treatment. The 2 preparations of nifuratel, on the other hand, gave rise to few unwanted effects and also interfered less with the bacterial flora of the bowel, thus reducing the risk of reinfection with resistant organisms (Brumfitt, unpublished data). Further, the lack of toxicity makes these drugs particularly useful for the treatment of bacteriuria in pregnancy. Our results are remarkably similar to those of the preliminary studies reported by Tynan, Macis and Ward-MacQuaid (1969).

Summary

A total of 120 patients, including 53 pregnant women with significant bacteriuria, received 163 7-day courses of oral antimicrobial agents allocated in a randomised manner. The cure rates after 6 weeks' follow-up ranged from 73% to 86%, and there was no statistical difference between preparations of ampicillin, carbenicillin indanyl ester, and 2 different formulations of nifuratel. Side-effects occurred in 30% to 40% of the courses of penicillin drugs, but in under 15% of the course of nifuratel.

It is concluded that the new oral preparation of carbenicillin is a useful addition to the list of antimicrobial agents which are effective in the treatment of urinary infections in domiciliary patients. Furthermore, nifuratel has been confirmed as a highly active non-toxic drug which is valuable in the treatment of urinary infections.

We would like to thank our clinic nurses and secretaries, particularly Mrs G. M. Brown, Mrs M. Ratcliffe and Mrs S. Terry for valuable assistance, and Mrs Italia Franklin who performed most of the technical work in this study.

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Book Reviews

Cornell Seminars in Nephrology. Edited by E. Lovell Becker. Pp. 260+xii with numerous illustrations. New York: John Wiley and Sons, 1973. £10·85.

This book is based on a series of seminars held at The New York Hospital—Cornell Medical Centre. Although about a third of the text is devoted to glomerulonephritis, the book embraces a wide range of topics including acute and chronic renal failure, hypertension, vitamin D metabolism, developmental renal physiology, the effects of hypoxia on the kidney and idiopathic hypercalciuria. Many of the chapters are excellent and some, notably those on focal glomerular sclerosis, post-streptococcal glomerulonephritis, vitamin D metabolism and acute renal failure, are models of authority and clarity. However, despite this and despite the distinction of many of the authors, the book as a whole is disappointing. It lacks the cohesion and purpose of a more conventional textbook and many readers will be irritated by the variations in the standards of the contributions, some of which are clearly intended for undergraduates and others for postgraduates, and by the somewhat haphazard arrangement of the topics.

A. R. H.

Trimethoprim-Sulphamethoxazole: Microbiological, Pharmacological and Clinical Considerations. Edited by M. Finland and E. Kass, 1st Edition. Pp. 384. London: University of Chicago Press, Ltd., 1973. £9·00.

This book is based on the proceedings of a symposium on trimethoprim-sulphamethoxazole (cotrimoxazole) held in Boston, Massachusetts, in 1972 with the addition of several papers, and has previously been published in a supplement to the November 1973 issue of the *Journal of Infectious Diseases*. The overall standard of the papers is very high, which is to be expected with Drs Maxwell Finland and Edward Kass chairing the symposium and editing this publication. The first two papers by G. H. Hitchings and J. J. Burchall show very clearly that the selective toxicity of trimethoprim for bacteria is due to its greater affinity for bacterial than mammalian dihydrofolate reductase and that its activity is markedly enhanced by the action of sulphonamide. It is a great step forward in the development of scientific medicine when a new therapeutic agent is presented to the medical profession with such detailed information on its mechanism of action and accompanied by the necessary clinical trials of its use in man. There are 13 papers on *in vitro* microbiological studies, 7 on metabolism and pharmacokinetics, and 2 on toxicology. This is followed by a large number of papers on clinical experience in paediatrics, bacterial infections of the genito-urinary system including gonorrhoea and prostatitis, and infections of the respiratory and gastro-intestinal tracts. There is a short but pertinent and adequate discussion after each section. The refreshing aspect of these papers which particularly applies to urinary tract infections, is the number of controlled clinical studies presented from Britain, America, Japan and France. There is clear evidence from these studies that in complicated or upper urinary tract infections the use of the combination of trimethoprim and sulphonamide is superior to the use of either agent alone. The paper by Stamey, Bushby and Bragonje on the diffusion of trimethoprim from serum into prostatic fluid brings new hope to the treatment of prostatitis and this is supported by two preliminary clinical reports. Finally there is a valuable review of the present position of cotrimoxazole by Brumfitt, Hamilton-Miller and Kosmidis and a critical analysis and commentary on the conference by its two chairmen. This book would be of value to every academic department of urology, since it will furnish the reader not only with the evidence for today's chemotherapeutic practice, but also with the standard of presentation of a new therapeutic agent that we should demand in the future.

J. B. S.

Erratum

In the paper by J. Chesney, pages 209-218, in the April issue of the *British Journal of Urology*, there were 2 errors. Table II, second line should read 62, not 52. Table III, calcification, first column should read Number of Patients *without* calcification. We apologise for these errors.

Conferences and Courses

LIVERPOOL UNIVERSITY AND LIVERPOOL REGIONAL UROLOGICAL CENTRE

A week's course in Special Aspects of Urology will be held from 22nd to 27th September 1975.

Paediatric Urology, Paraplegic Urology, Male Infertility, Genito-Urinary Tuberculosis, Renal Failure and Transplantation.

Distinguished guest speakers will take part and the course is approved under the Advanced Postgraduate Training Scheme for senior trainees and consultants. (Under this Scheme the D.H.S.S. reimburses Regional Health Authorities and Teaching Authorities in England and Wales, course fees, travelling and subsistence expenses and the cost of a necessary locum. Enquiries about eligibility should be addressed to the employing authority.)

Further information regarding the details of the course may be obtained from:

Mr N. O. K. Gibbon, Liverpool Regional Urological Centre, Sefton General Hospital,
Liverpool L15 2HE

IV EUROPEAN CONGRESS ON STERILITY

This Congress will be held in Madrid from October 6th-8th 1975.

There will be a section on Male Infertility.

Those interested in receiving the Preliminary Programme and information on participation should write to Dr. J. Cortes-Prieto, Puerto de Bermeo, 11. Madrid (34) Spain.

XVIIth CONGRESS OF THE INTERNATIONAL SOCIETY OF UROLOGY

This Congress has been arranged to take place in Johannesburg, South Africa, from the 25th to 30th July 1976

The themes to be discussed are Tumours of the Kidney, Neurogenic Bladder, Male Infertility, Isotopes in Urology, and Management of Traumatised Urethra.

Members of the International Society of Urology have been notified and will have indicated an intention to attend.

A limited number of non-members may attend as observers and should contact the national delegate(s) of the respective country for permission to attend.

Congress address: Festivals & Conventions Trust, P.O. Box 61326, Marshalltown 2107, Transvaal, Republic of South Africa.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The list of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal*, *i.e.* in anatomical order beginning with papers on the kidney.

A general section is included at the end.

KIDNEY

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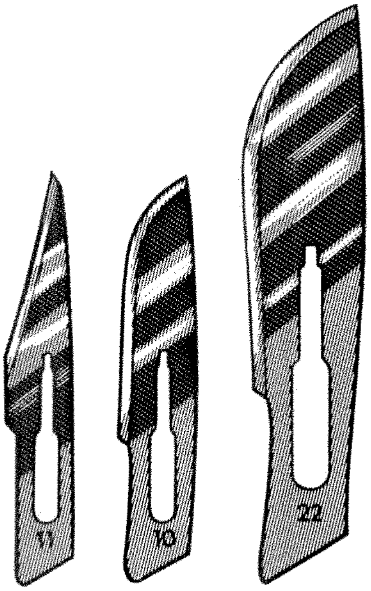

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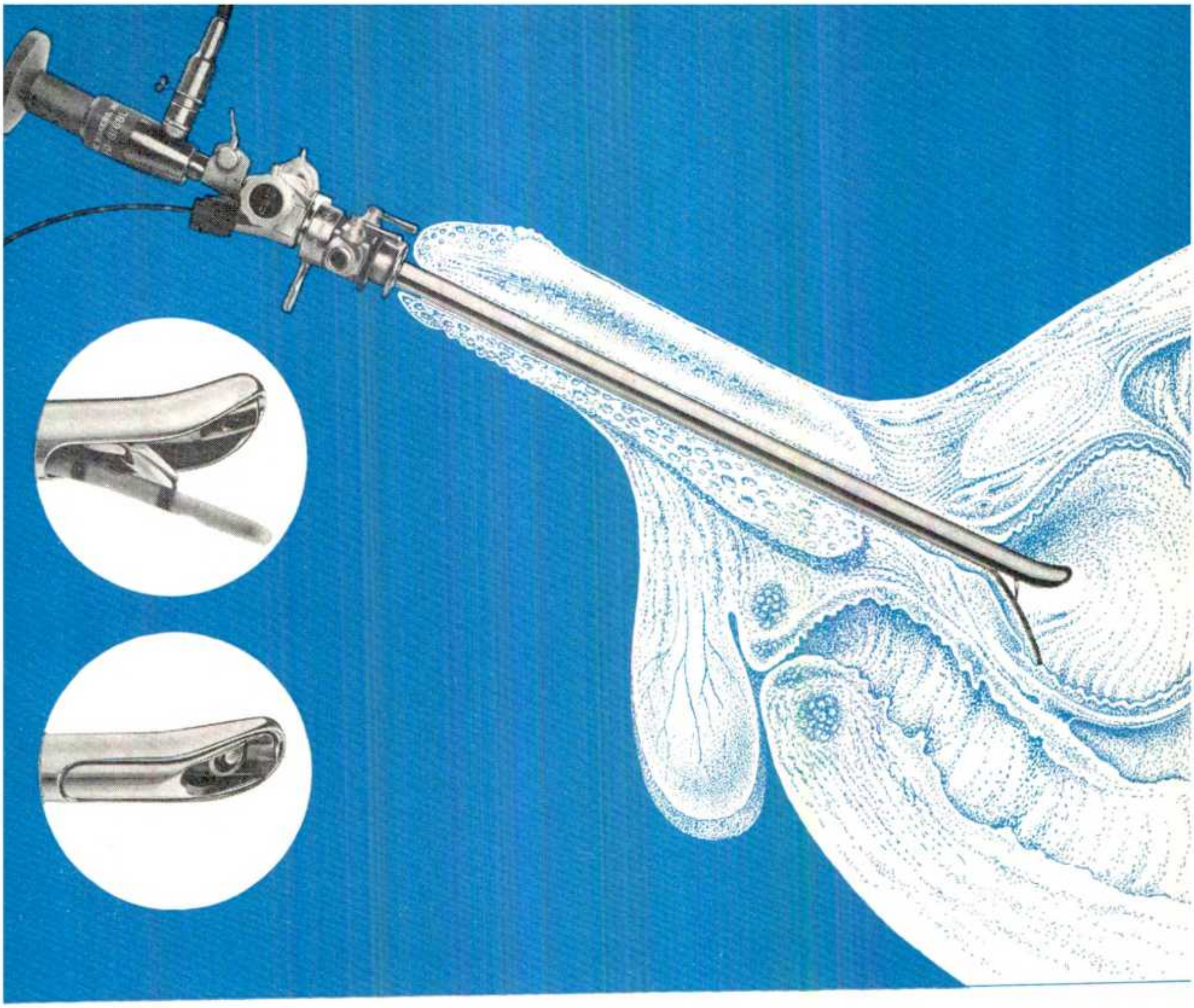

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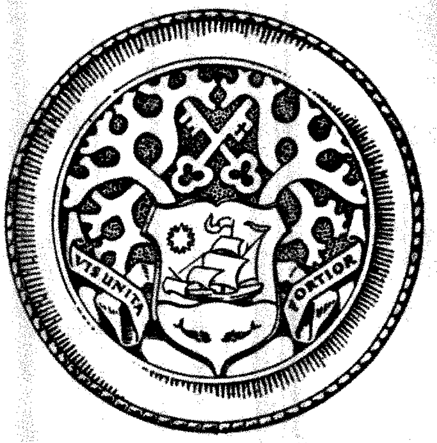

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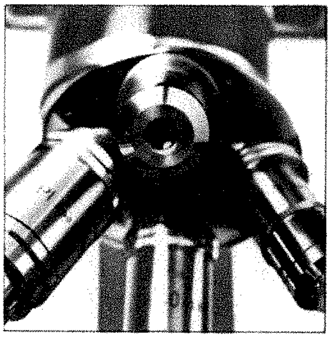

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1. 'Antibiotics under the microscope.' A film freely available to the medical profession.
2. Brit. med. J., (1972), 3, 13.
3. Curr. Med. Res. & Opin., (1972), 1, 10.
4. Brit. J. Dis. Chest., (1972), 66, 185.
5. Lancet, (1975), 505.

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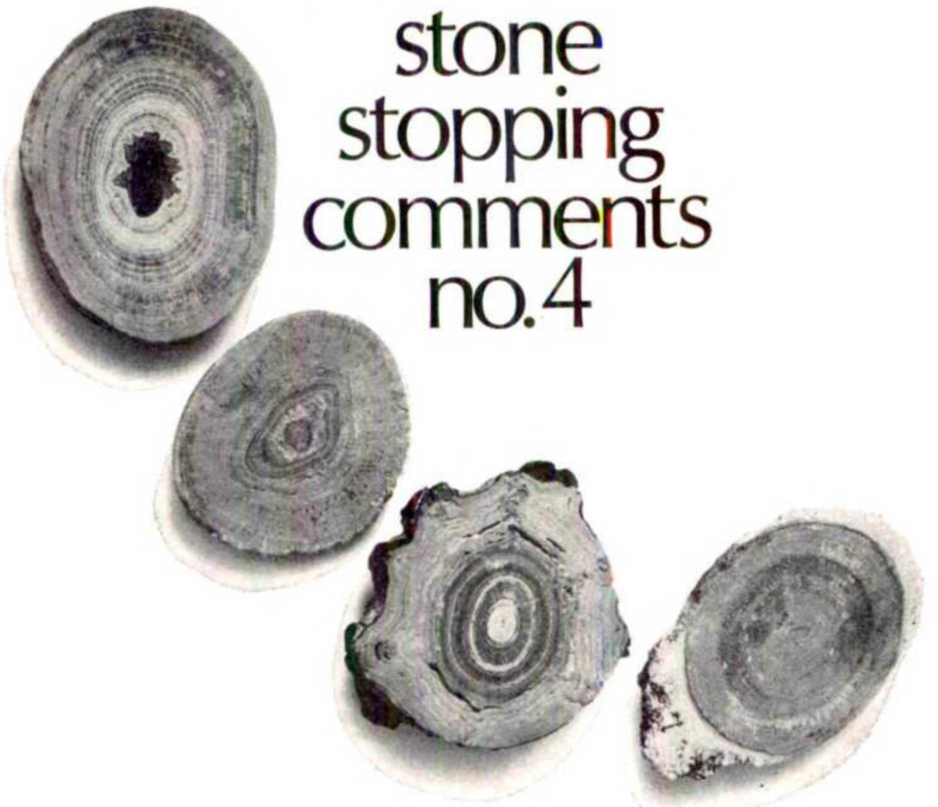

stone stopping comments no.4

In a recent study[1] measurements of ^{47}calcium and of urinary calcium excretion were made in 125 cases of urolithiasis (78 solitary stone, 47 recurrent).

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1. Brit J Urol, (1974) **46**: 377-384.
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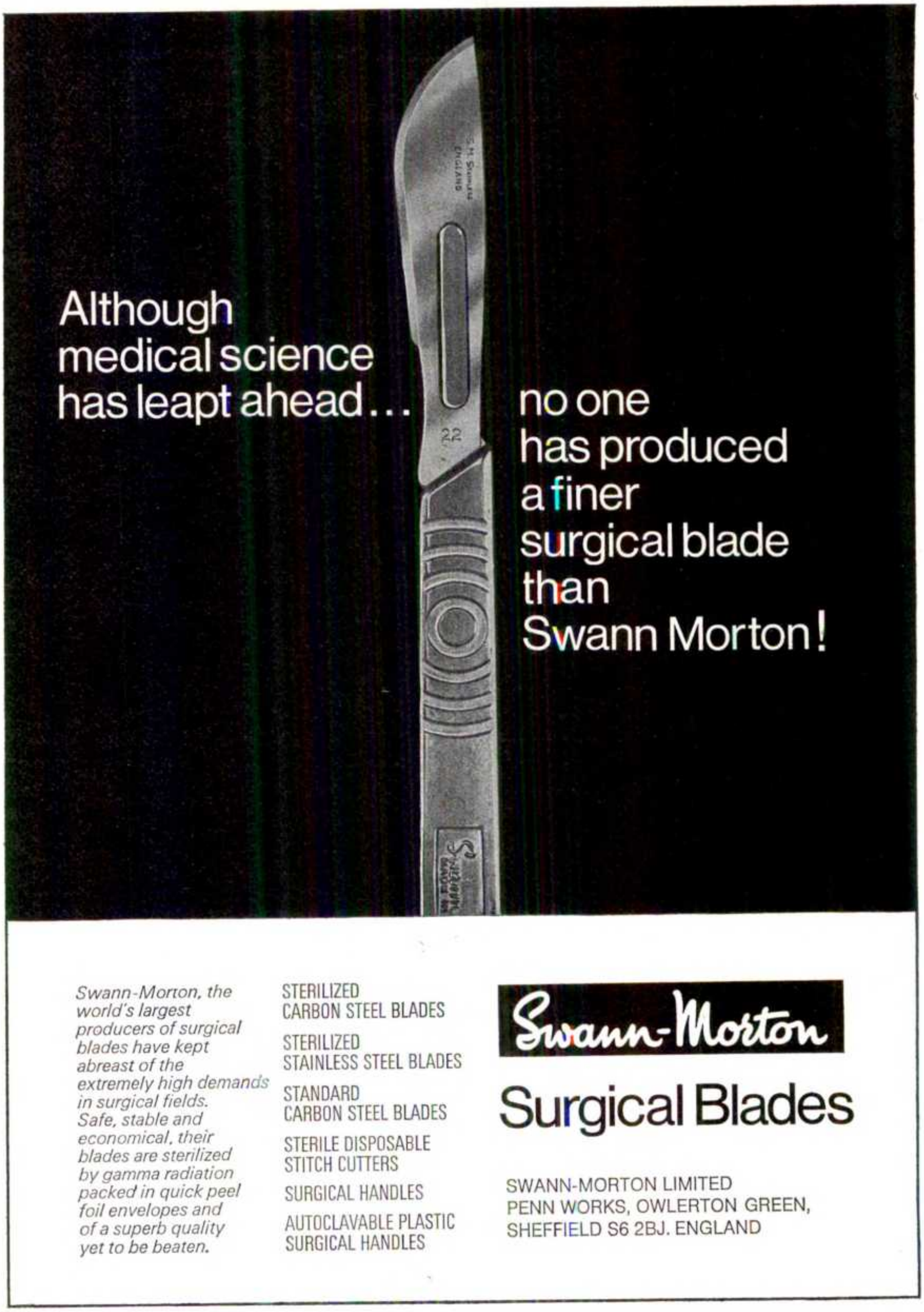

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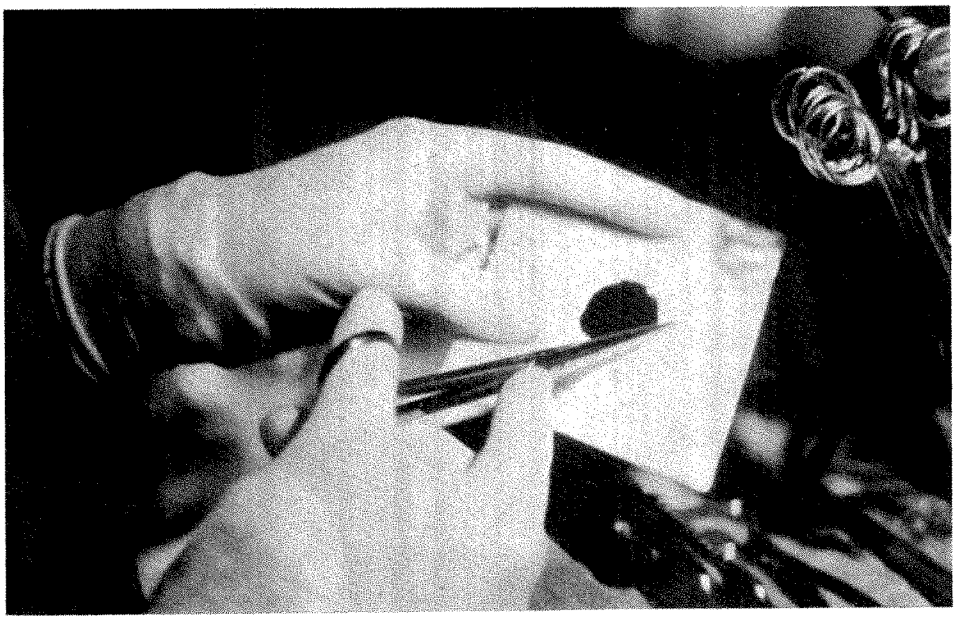

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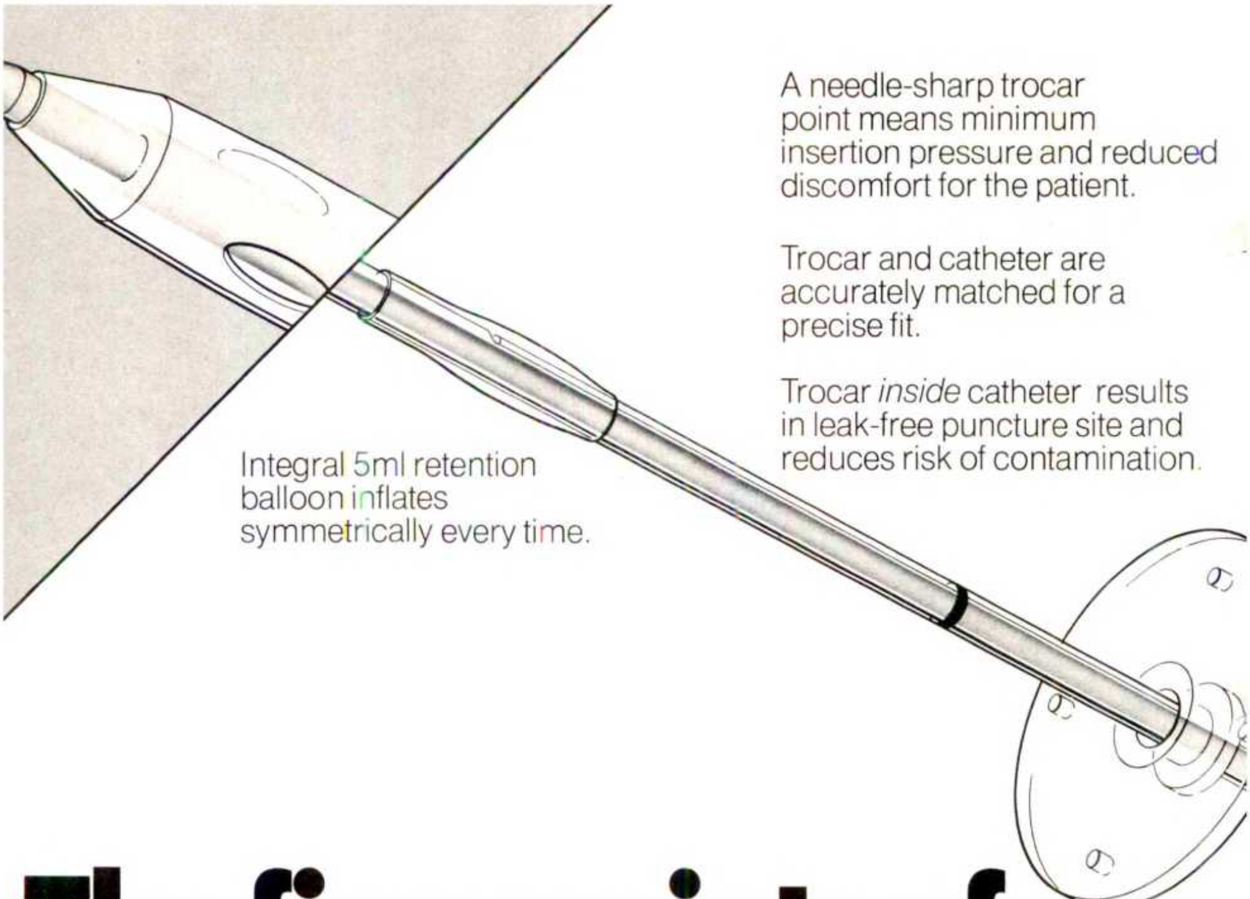

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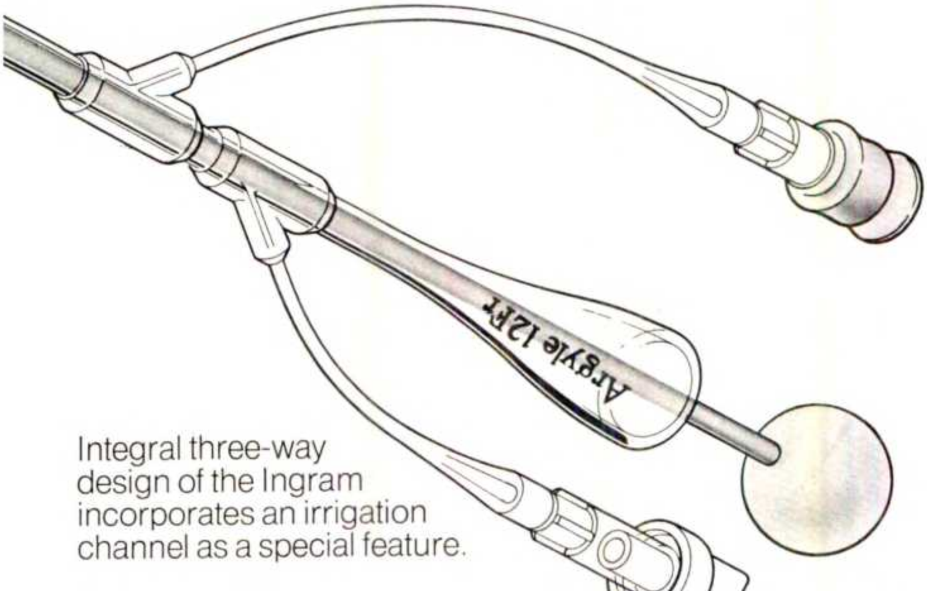

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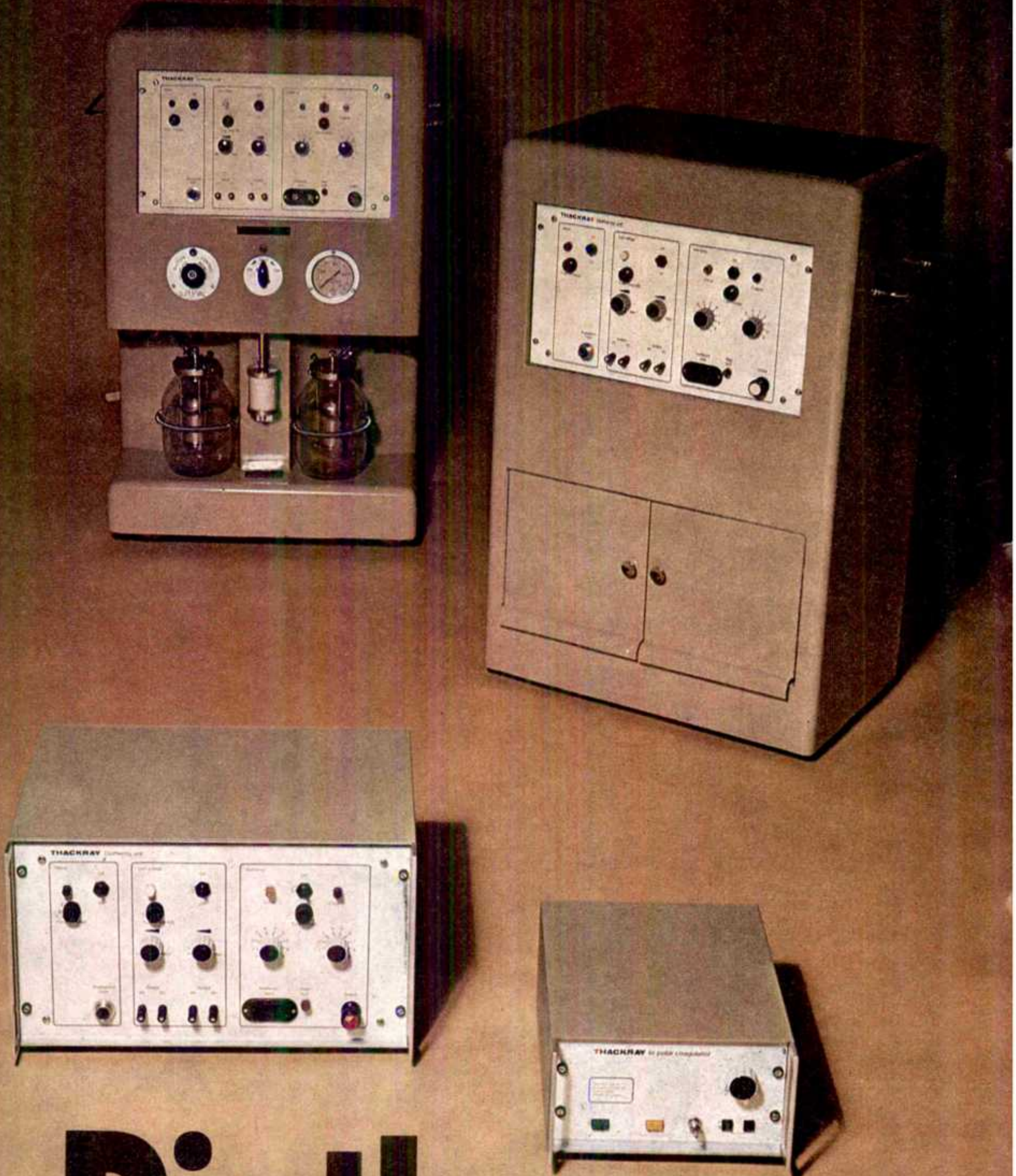

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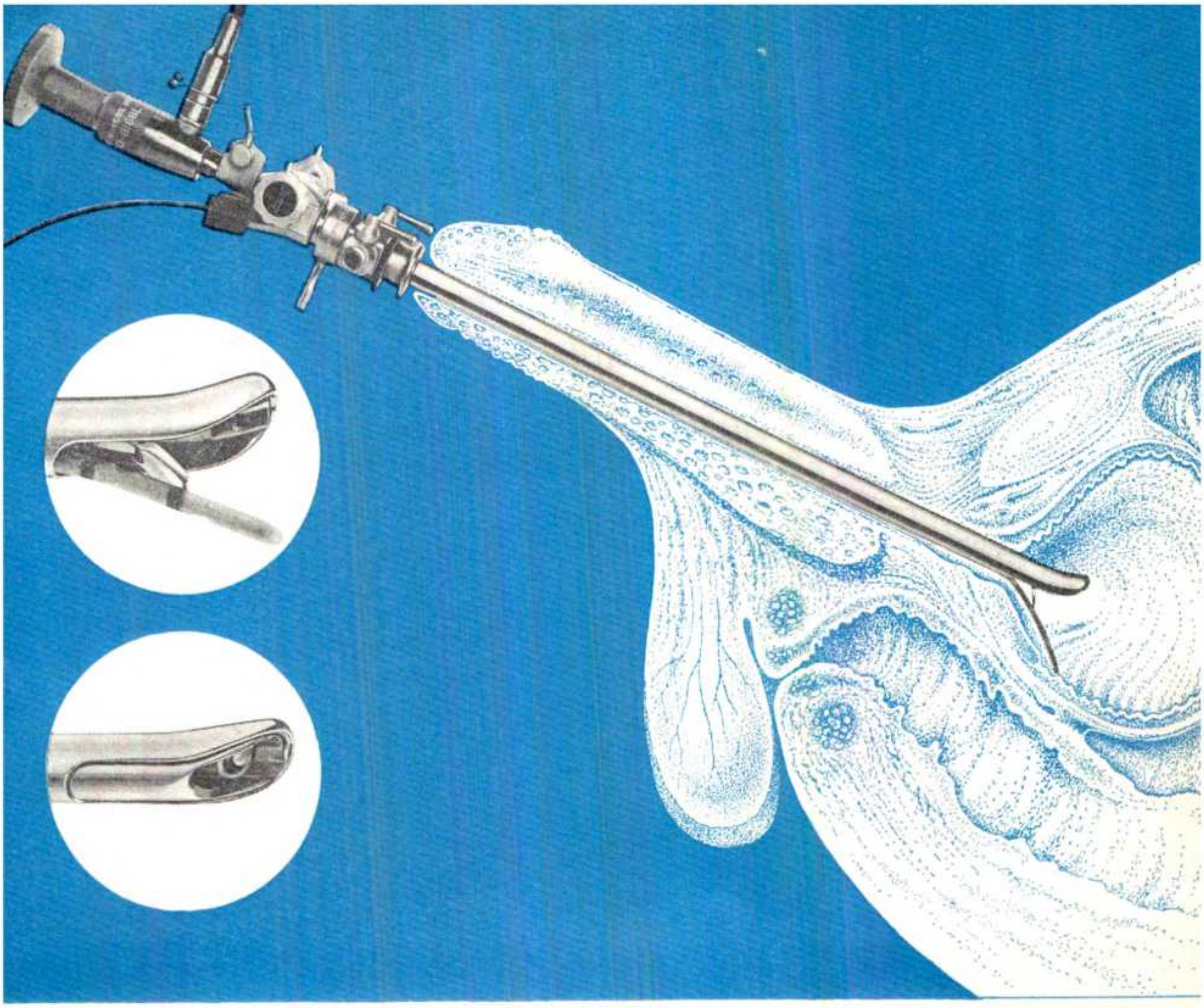

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A Computer-based Record and Organisation System for a Department of Urology

J. E. A. WICKHAM, C. A. C. CHARLTON, B. RICHARDS, W. F. HENDRY, J. P. WARD, E. P. N. O'DONOGHUE, R. G. HAMSHERE and D. A. FRANKLIN
Department of Urology, St Bartholomew's Hospital, London

In 1968 a 2-consultant Department of Urology was set up at St Bartholomew's Hospital, London. An allocation of 20 beds was made, 17 male and 3 female, with access to 6 day-ward beds on 2 days per week. An opportunity was thus presented to organise an efficient urological service for the hospital. To achieve this, two points seemed to be of primary importance.

Firstly, the aim was to provide an organisation for the rapid and comfortable passage of the patient with urological disease from the community environment, through the technical facilities of the department, and back to the community as soon as possible. A proportion of patients with malignant and other disease requiring perpetual follow-up would become an ongoing work load commitment of the department.

Secondly, it seemed essential to build into the organisation some mechanism for self-assessment of the medical and clinical efficiency of the unit so that the efforts of our department could be compared against the published standards for care and cure of patients in other urological units. For example, it seemed important to have readily available detailed information of the survival rates for patients with different clinical and pathological stages of bladder carcinoma.

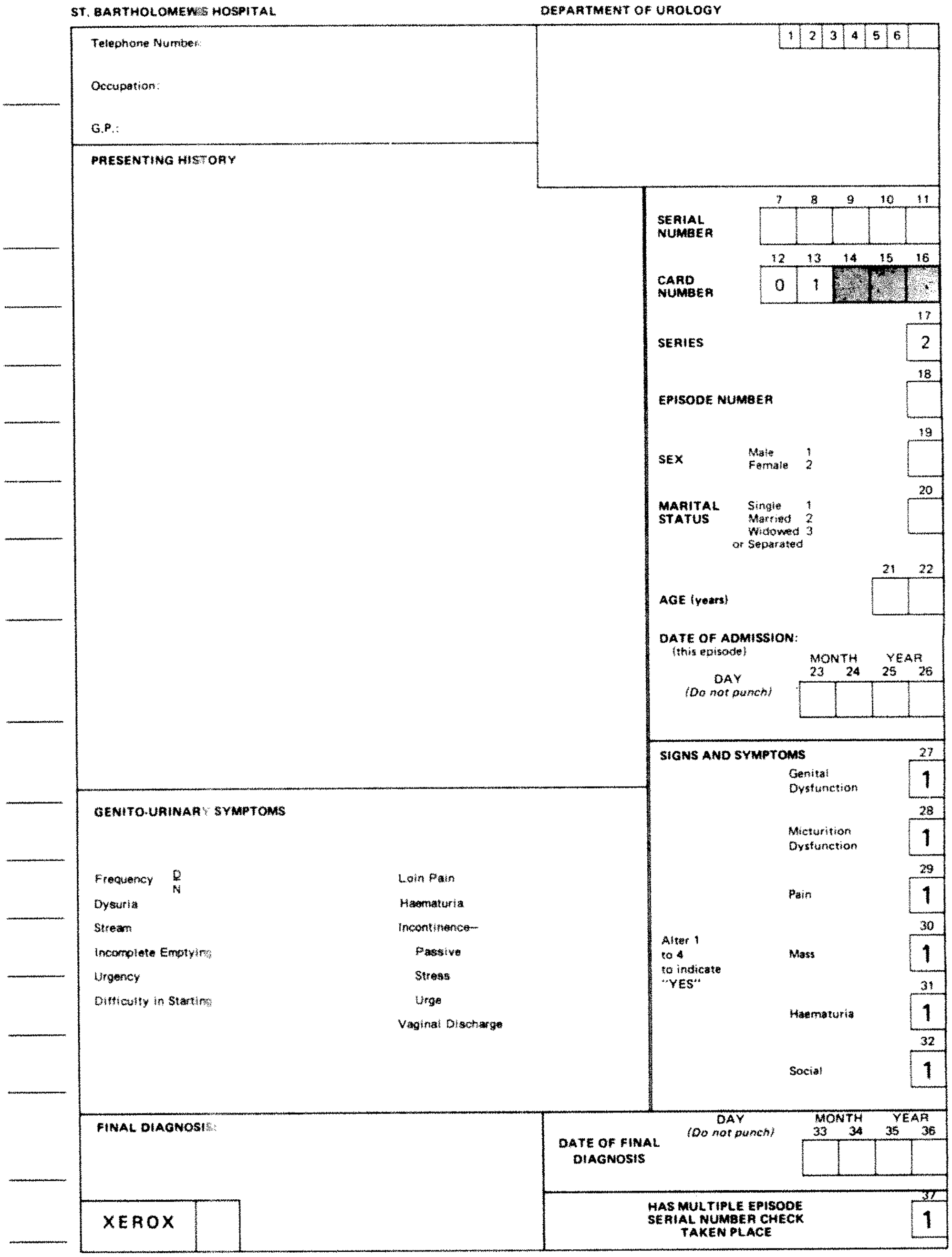
Both of these considerations predicated a need for an efficient and practicable record system, preferentially computer based, for rapidity of data handling. We were fortunate that at about this time a Computer Department had been established at the hospital and the Director of this Unit was consulted at an early stage in our deliberations. Enquiries were initially made at a number of hospitals and University Departments as well as at the Department of Health as to previous experience in this field. We were interested to find, however, that although considerable effort had gone into diagnostic studies and into the *administrative* handling of case records by computer, little work had been done on the comprehensive organisation of clinical data. Only one unit at that time, in the Western Infirmary in Glasgow, had even approached the problem (Kennedy *et al.*, 1968), and that study was restricted to one disease entity, peptic ulceration. In other countries, various centres have experimented with clinical data handling; for example, Levy, Cammarn and Smith in Cleveland, U.S.A. (1964), described the computer handling of clinical records of a diabetic clinic and Slack *et al.* (1966) described a computer system for medical history taking. Schenthal, Sweeney and Nettleton (1960) described and used a computer system for clinical data handling and rapid retrieval in New Orleans, with some success. A computer survey in a department of Paediatric Urology was used in Tauranga, New Zealand, by Watts (1974) but this was a retrospective study.

Methods

We therefore attempted, for our own department, a computerised case record system to incorporate an on-going flow sheet for day-to-day clinical use, coupled with facilities to focus in detail upon a limited number of clinical problems.

The system finally resolved itself into 3 principal parts:

1. A master identification sheet for each new patient coming under the care of the Unit.



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AGE (years) 21 22

DATE OF ADMISSION: (this episode) DAY (Do not punch) MONTH 23 24 YEAR 25 26

SIGNS AND SYMPTOMS

Alter 1 to 4 to indicate "YES"

27	Genital Dysfunction	1
28	Micturition Dysfunction	1
29	Pain	1
30	Mass	1
31	Haematuria	1
32	Social	1

GENITO-URINARY SYMPTOMS

Frequency D N	Loin Pain
Dysuria	Haematuria
Stream	Incontinence—
Incomplete Emptying	Passive
Urgency	Stress
Difficulty in Starting	Urge
	Vaginal Discharge

FINAL DIAGNOSIS:

DATE OF FINAL DIAGNOSIS DAY (Do not punch) MONTH 33 34 YEAR 35 36

HAS MULTIPLE EPISODE SERIAL NUMBER CHECK TAKEN PLACE 37: 1

XEROX

Fig. 1

2. A series of detailed sub-cards for intensive study of specific disease entities.
3. Related computer punch cards for the master card and each sub-card.

At no stage was it intended to use the computing facility as a diagnostic aid.

A. The Master Sheet. The final format of this sheet was arrived at after nearly 18 months of effort on the part of all members of the project and is illustrated in Figure 1. It contains a distillation of all data that was considered essential to record, to process the patient and his disease through the departmental machinery adequately. A constant vigilance was kept to exclude useless information and to construct a system that would be practicable for day-to-day use by a changing population of medical staff. We felt it was vital that such a system should cause only minimal irritation and added burden to the staff otherwise the basic information would be incompletely and inaccurately recorded.

A too detailed computer record system in another hospital was seen to have foundered because of its complexity.

(a) Features of the Sheet. 1. Identification details of the patient are recorded by the Clinic Clerk at the top of the sheet such as address, age, sex, etc., and these are then coded in the appropriate computer boxes together with the patient's hospital number.

Space is then provided for long-hand recording of the patient's clinical history.

2. The relevant urological symptoms and signs are documented and then translated to appropriate adjacent computer boxes. Surprisingly, all relevant urological data can be fully recorded in only 6 computer boxes.

3. **Classification of organ and pathology** (Fig. 2). When the patient has been fully investigated and treated a further group of boxes are completed appropriately to record the organ involved and the pathological nature of the disease process.

4. **The basic type of treatment** administered is then noted in a further group of boxes.

5. **Sub-card boxes.** If the patient has been diagnosed as suffering from a disease entity for which obligatory follow-up is required, *e.g.* cancer of the bladder, this fact is recorded in the appropriate box. Likewise boxes are completed for those patients whose follow-up is indicated because of an ongoing research interest within the department.

6. **Surgeon and hospital.** The operating surgeon or the hospital concerned are then recorded.

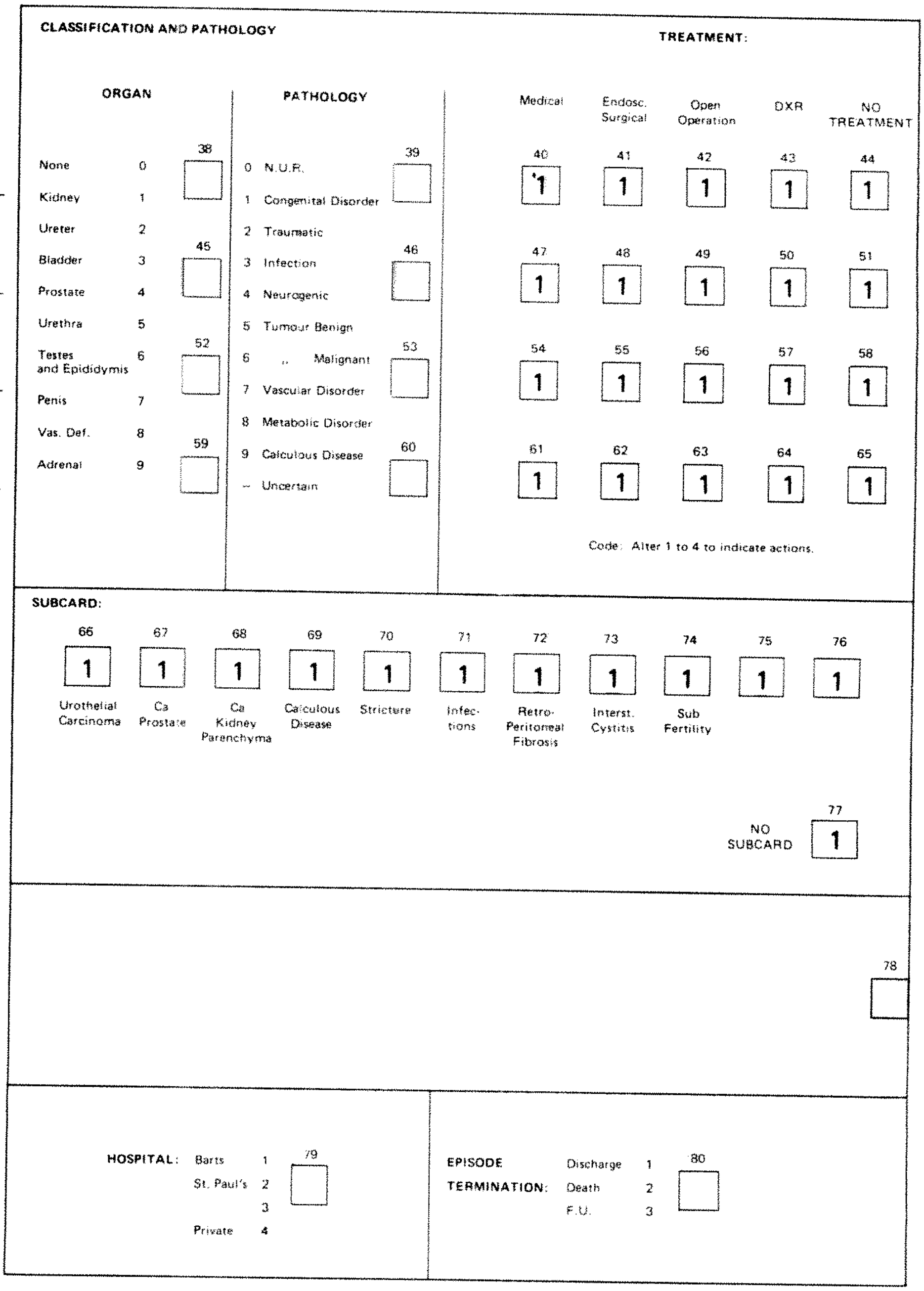
7. **The episode termination.** This we have found is the key box to the whole system. Here the decision must be made by the doctor either that the patient is to be followed up or discharged. It has been a strict policy that unless there is some considerable indication as to why the patient should be followed up, then he should be returned by way of his G.P. to the community as soon as possible. Follow-up is allowed only for obligatory conditions such as carcinoma of the bladder or where some particular facet of the disease or treatment is being investigated prospectively by a member of the department. All other patients *must* be discharged and the patient's own doctor fully informed of this fact.

(b) Manipulation of Data once Collected. Once the master sheet has been completed by the member of staff concerned, either at the completion of the out-patient attendance and treatment or following definitive in-patient investigation and treatment, the notes are passed to the Unit Secretary. The master sheets are then photocopied and the notes returned to the hospital record stacks. The photocopy of the master sheet record is then passed to the computer department, where appropriate computer cards are punched and the data is finally transferred to a magnetic tape-store (Fig. 3) provided that it passes a number of checks first. Automatic validation of data in an exercise of this kind is essential, especially with a changing population of junior medical staff filling in the forms. Error checking includes confirming that the codes recorded for each item are within the valid range for that item, and also cross-checking for coding between items—*e.g.* "female", benign prostatic hypertrophy or vasectomies, follow-up without a sub-card, omission of treatment or sub-card details, duplication of serial or hospital numbers, etc. Erroneous records are returned to the Department of Urology for correction. It has been a cardinal principle of the exercise that all errors, no matter how obvious or trivial, shall be corrected by the clinical department concerned rather than by the Computing Unit. The photocopy sheets are also kept by the department for future reference if further long-hand details should need to be extracted from the sheets. This method saves a continual extraction of notes from the main hospital record stacks. The department is thus left with an independent and immediate access record on magnetic tape of all patients that have been processed by the department.

B. Sub-cards. Basic information about patient and disease is provided by the master sheet. If, however, the diagnosed disease is such that indefinite care by the department is obligatory, as with cases of malignant disease of the bladder, then subsidiary or sub-card documentation is carried out for the patient. This initiation is indicated by positive action in the appropriate sub-card box on the master sheet and in the episode termination box. On the appropriate sub-card, a further, far more detailed analysis of the patient's condition is laid out again in a form amenable to computer assessment. Sub-card 1 (Fig. 4) is shown as an example which has been developed for carcinoma of the bladder.

The other circumstance in which a sub-card follow-up is initiated is when a member of the department is involved in a long or short-term investigation of a patient or treatment of his disease as a prospective research analysis. Such a sub-card has been developed for the initial assessment of patients treated for renal calculus disease by regional hypothermia (see Fig. 5). Other cards are in preparation for other projects. Thus only two circumstances qualify a patient for positive follow-up in the department.

1. Obligatory because of the nature of his disease.
2. Prospective because of a research interest by the department.



CLASSIFICATION AND PATHOLOGY

ORGAN

None	0	38 ☐
Kidney	1	
Ureter	2	
Bladder	3	45 ☐
Prostate	4	
Urethra	5	
Testes and Epididymis	6	52 ☐
Penis	7	
Vas. Def.	8	
Adrenal	9	59 ☐

PATHOLOGY

0	N.U.R.	39 ☐
1	Congenital Disorder	
2	Traumatic	
3	Infection	46 ☐
4	Neurogenic	
5	Tumour Benign	
6	,, Malignant	53 ☐
7	Vascular Disorder	
8	Metabolic Disorder	
9	Calculous Disease	60 ☐
–	Uncertain	

TREATMENT:

Medical	Endosc. Surgical	Open Operation	DXR	NO TREATMENT
40 1	41 1	42 1	43 1	44 1
47 1	48 1	49 1	50 1	51 1
54 1	55 1	56 1	57 1	58 1
61 1	62 1	63 1	64 1	65 1

Code: Alter 1 to 4 to indicate actions.

SUBCARD:

66	67	68	69	70	71	72	73	74	75	76
1	1	1	1	1	1	1	1	1	1	1
Urothelial Carcinoma	Ca Prostate	Ca Kidney Parenchyma	Calculous Disease	Stricture	Infections	Retro-Peritoneal Fibrosis	Interst. Cystitis	Sub Fertility		

NO SUBCARD 77 1

78 ☐

HOSPITAL: 79 ☐

Barts 1
St. Paul's 2
3
Private 4

EPISODE TERMINATION: 80 ☐

Discharge 1
Death 2
F.U. 3

Fig. 2

All other patients are returned to their doctor.

The decision to follow-up a patient or return him to the community is made by the individual member of the department completing the episode termination box on the master sheet at the time of the final discharge letter summary. In most cases this decision is straightforward, but difficult problems are referred to the consultants for consideration at a weekly meeting of the departmental staff.

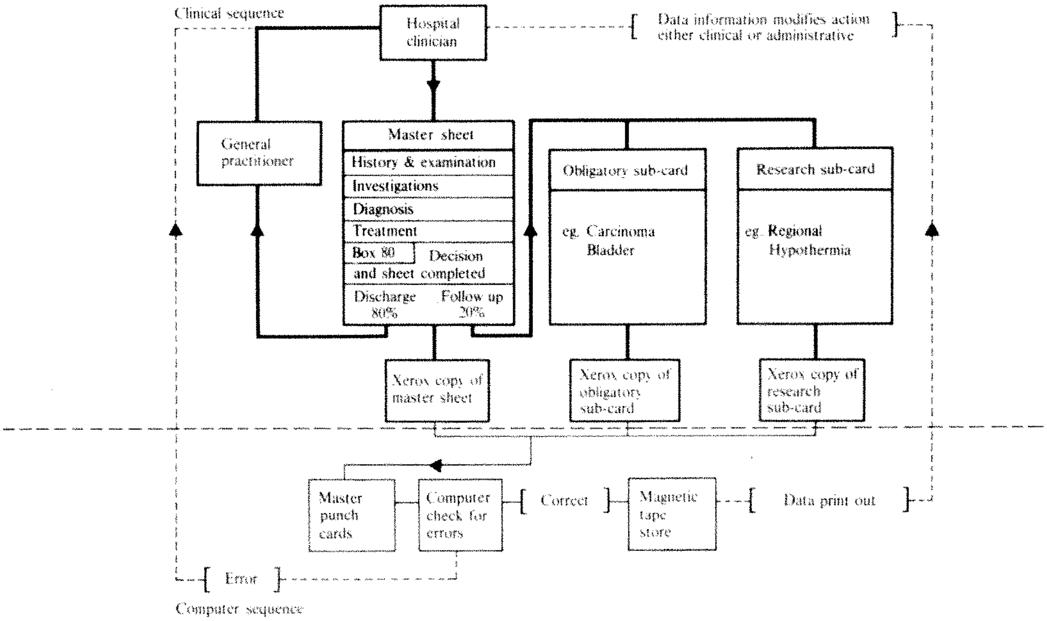


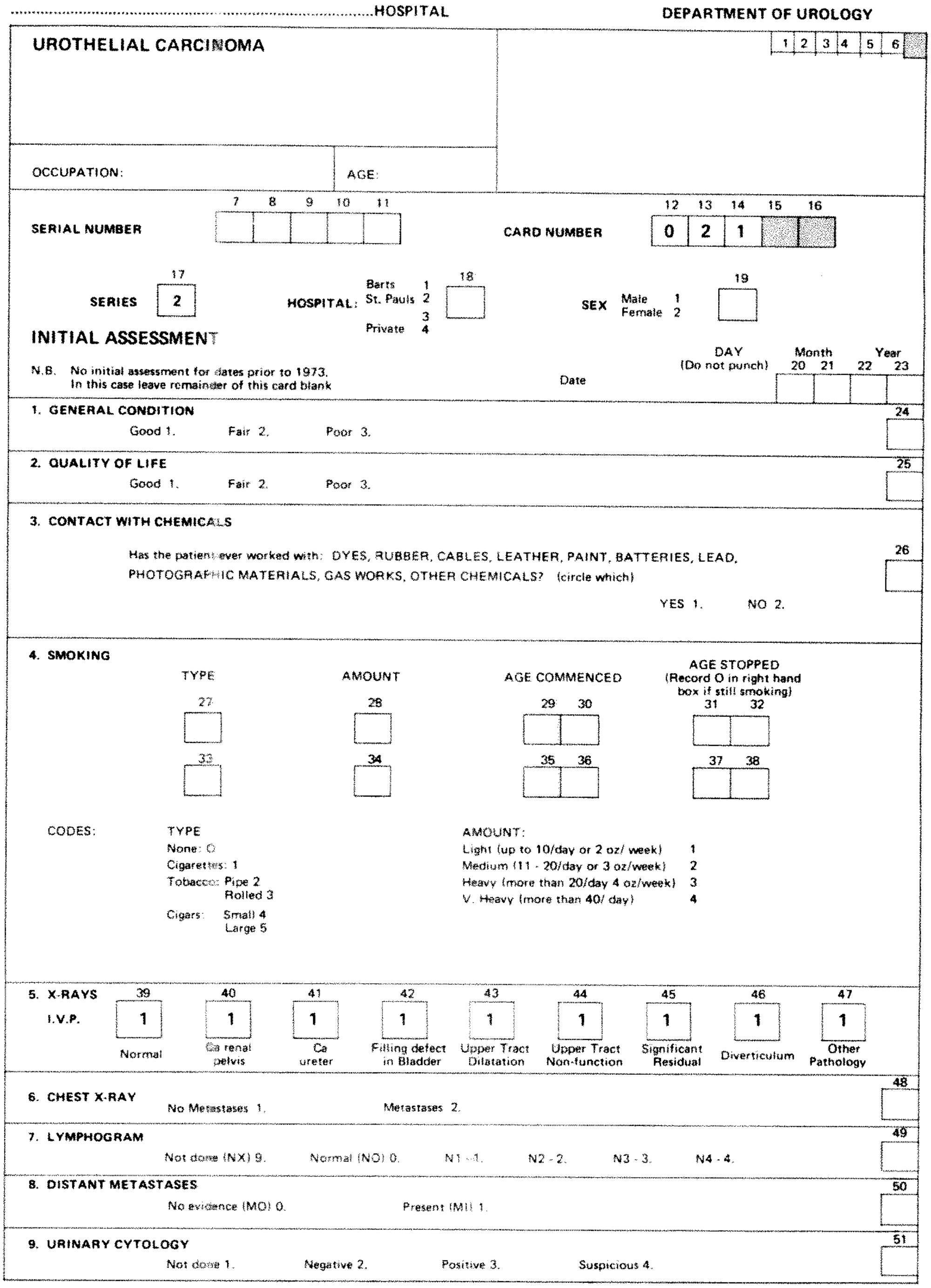
Fig. 3

Results

A. The Advantages of this System. After 4 years' complete application of this system, 2 principal advantages emerged.

1. **The effect on follow-up numbers.** It was found, to our great satisfaction, that the large number of patients who used to attend our out-patient clinics for follow-up declined dramatically. From a biweekly follow-up of about 60 or 70 patients we have now reduced our clinic list to something of the order of 40 patients. This we consider has been entirely due to the fact that each doctor has to make a definitive mental decision about each patient at the end of his processing period (Box 80). Vague follow-up appointments to "see how you are in 3 months or so" have been abolished. Either the patient is surgically ill enough to require hospital treatment of the technical nature offered by our department when the episode is obviously not terminated, or he is well enough to return to the community or to the care of his own general practitioner. We feel that it is an act of mental sloth if a hospital doctor does not make such a definitive decision when all investigatory facts are at his disposal. Many patients are unnecessarily invited back to the hospital year after year at considerable cost to the Health Service for a semi-social chat which could have been very well conducted by their own general practitioner.

We consider that the most important root cause of this phenomenon is *poor consultant supervision of the department.* Many junior doctors are reluctant to discharge patients because of inexperience and because they are unable to make difficult decisions which should and must be made by the managing consultant. If, however, the consultant is overburdened with a plethora of follow-up patients then he is precluded from performing in his advisory capacity and a vicious circle is established (Fig. 6).



....HOSPITAL

DEPARTMENT OF UROLOGY

1	2	3	4	5	6

UROTHELIAL CARCINOMA

OCCUPATION:

AGE:

SERIAL NUMBER 7 8 9 10 11

CARD NUMBER

12	13	14	15	16
0	2	1	▨	▨

SERIES 17 [2]

HOSPITAL: Barts 1, St. Pauls 2, 3, Private 4 — 18

SEX Male 1, Female 2 — 19

INITIAL ASSESSMENT

N.B. No initial assessment for dates prior to 1973.
In this case leave remainder of this card blank

Date — DAY (Do not punch) — Month 20 21 — Year 22 23

1. GENERAL CONDITION — 24
Good 1. Fair 2. Poor 3.

2. QUALITY OF LIFE — 25
Good 1. Fair 2. Poor 3.

3. CONTACT WITH CHEMICALS — 26
Has the patient ever worked with: DYES, RUBBER, CABLES, LEATHER, PAINT, BATTERIES, LEAD, PHOTOGRAPHIC MATERIALS, GAS WORKS, OTHER CHEMICALS? (circle which)
YES 1. NO 2.

4. SMOKING

TYPE	AMOUNT	AGE COMMENCED	AGE STOPPED (Record O in right hand box if still smoking)
27	28	29 30	31 32
33	34	35 36	37 38

CODES:

TYPE
None: O
Cigarettes: 1
Tobacco: Pipe 2
Rolled 3
Cigars: Small 4
Large 5

AMOUNT:	
Light (up to 10/day or 2 oz/ week)	1
Medium (11 - 20/day or 3 oz/week)	2
Heavy (more than 20/day 4 oz/week)	3
V. Heavy (more than 40/ day)	4

5. X-RAYS I.V.P.

39	40	41	42	43	44	45	46	47
1	1	1	1	1	1	1	1	1
Normal	Ca renal pelvis	Ca ureter	Filling defect in Bladder	Upper Tract Dilatation	Upper Tract Non-function	Significant Residual	Diverticulum	Other Pathology

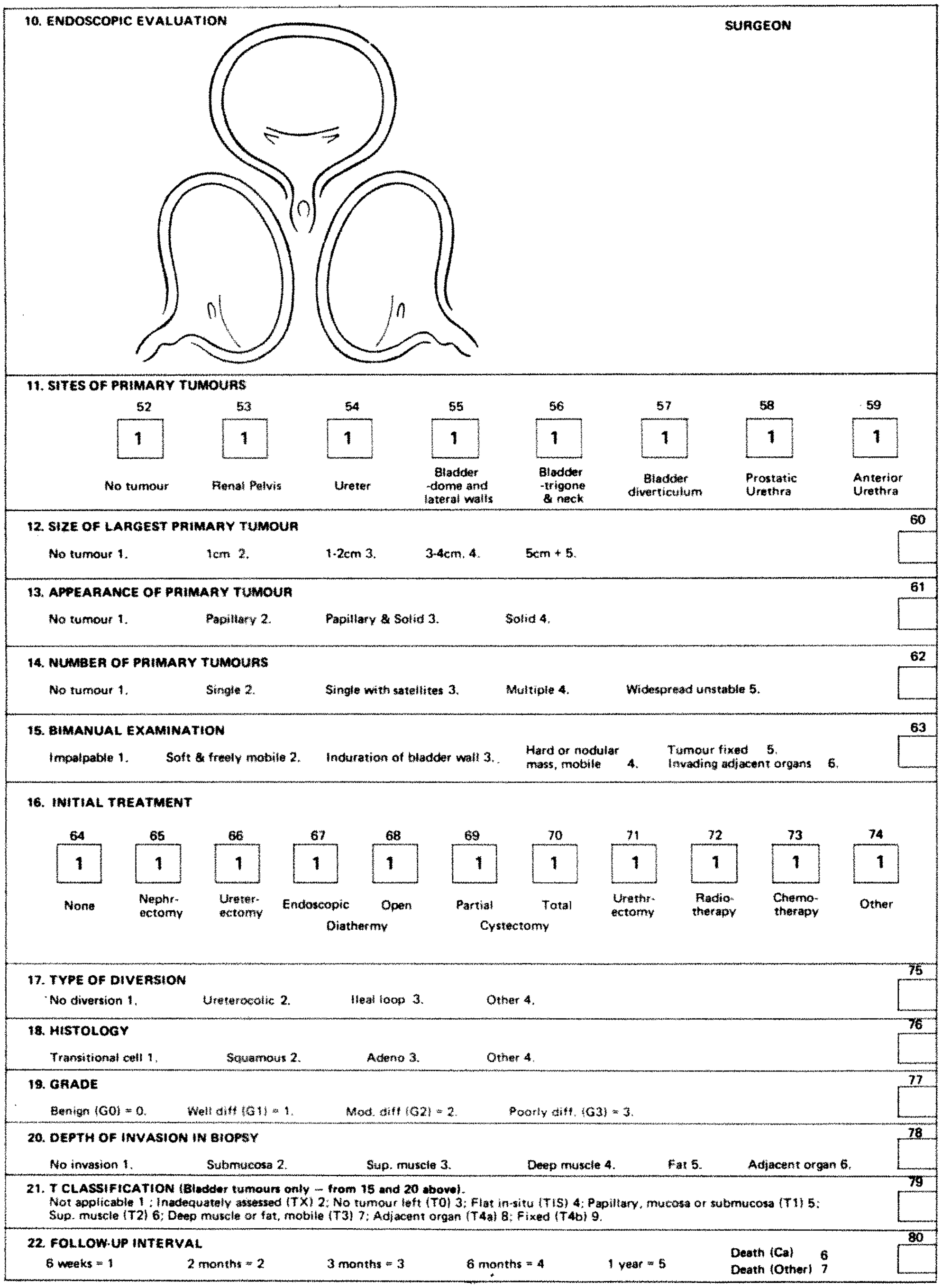
6. CHEST X-RAY — 48
No Metastases 1. Metastases 2.

7. LYMPHOGRAM — 49
Not done (NX) 9. Normal (NO) 0. N1 - 1. N2 - 2. N3 - 3. N4 - 4.

8. DISTANT METASTASES — 50
No evidence (MO) 0. Present (M1) 1.

9. URINARY CYTOLOGY — 51
Not done 1. Negative 2. Positive 3. Suspicious 4.

Fig. 4A



10. ENDOSCOPIC EVALUATION

SURGEON

11. SITES OF PRIMARY TUMOURS

52	53	54	55	56	57	58	59
1	1	1	1	1	1	1	1
No tumour	Renal Pelvis	Ureter	Bladder -dome and lateral walls	Bladder -trigone & neck	Bladder diverticulum	Prostatic Urethra	Anterior Urethra

12. SIZE OF LARGEST PRIMARY TUMOUR 60

No tumour 1. 1cm 2. 1-2cm 3. 3-4cm. 4. 5cm + 5.

13. APPEARANCE OF PRIMARY TUMOUR 61

No tumour 1. Papillary 2. Papillary & Solid 3. Solid 4.

14. NUMBER OF PRIMARY TUMOURS 62

No tumour 1. Single 2. Single with satellites 3. Multiple 4. Widespread unstable 5.

15. BIMANUAL EXAMINATION 63

Impalpable 1. Soft & freely mobile 2. Induration of bladder wall 3. Hard or nodular mass, mobile 4. Tumour fixed 5. Invading adjacent organs 6.

16. INITIAL TREATMENT

64	65	66	67	68	69	70	71	72	73	74
1	1	1	1	1	1	1	1	1	1	1
None	Nephrectomy	Ureterectomy	Endoscopic	Open	Partial	Total	Urethrectomy	Radiotherapy	Chemotherapy	Other
			Diathermy		Cystectomy					

17. TYPE OF DIVERSION 75

No diversion 1. Ureterocolic 2. Ileal loop 3. Other 4.

18. HISTOLOGY 76

Transitional cell 1. Squamous 2. Adeno 3. Other 4.

19. GRADE 77

Benign (G0) = 0. Well diff (G1) = 1. Mod. diff (G2) = 2. Poorly diff. (G3) = 3.

20. DEPTH OF INVASION IN BIOPSY 78

No invasion 1. Submucosa 2. Sup. muscle 3. Deep muscle 4. Fat 5. Adjacent organ 6.

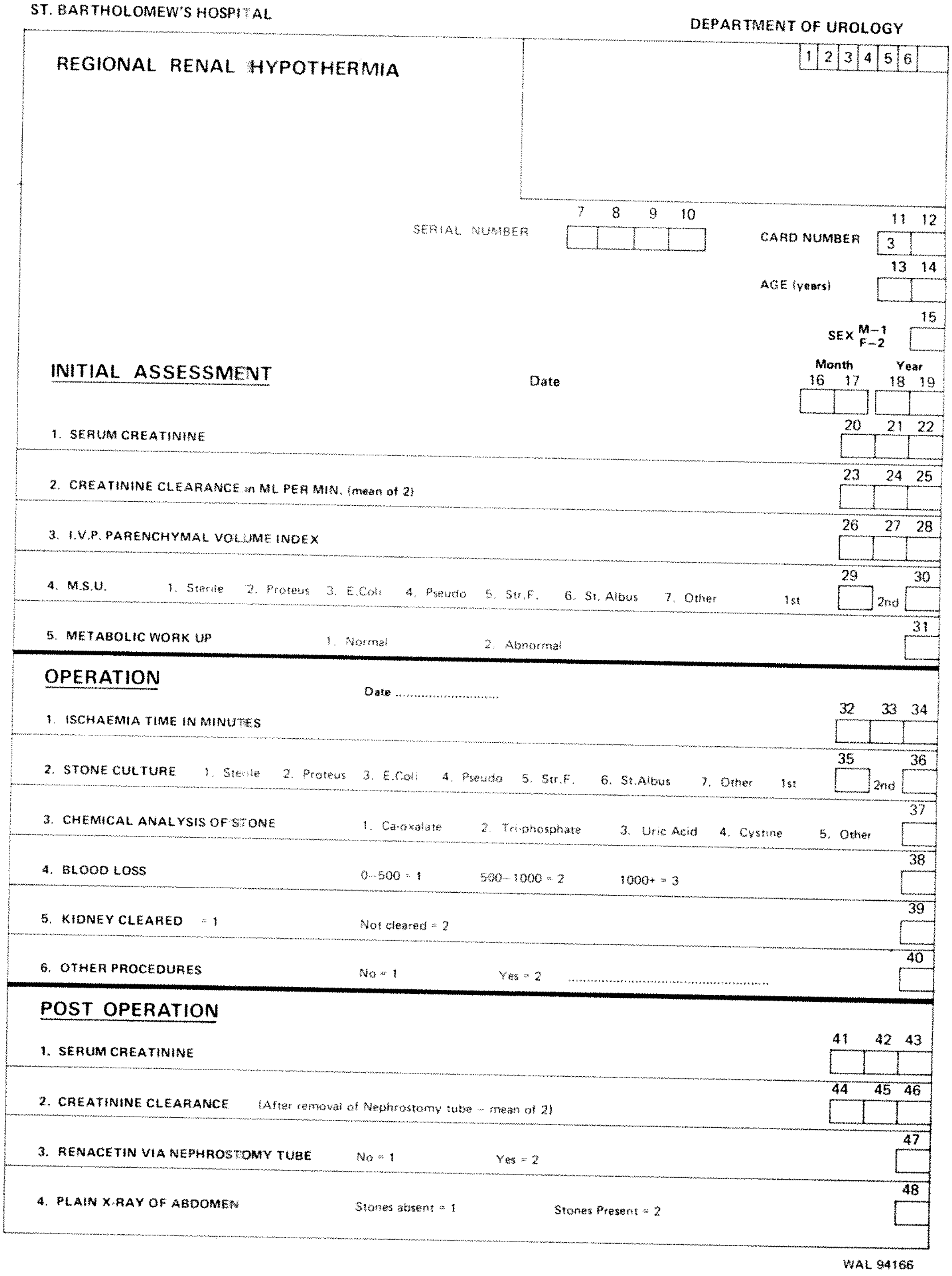
21. T CLASSIFICATION (Bladder tumours only – from 15 and 20 above). 79

Not applicable 1 ; Inadequately assessed (TX) 2; No tumour left (T0) 3; Flat in-situ (TIS) 4; Papillary, mucosa or submucosa (T1) 5; Sup. muscle (T2) 6; Deep muscle or fat, mobile (T3) 7; Adjacent organ (T4a) 8; Fixed (T4b) 9.

22. FOLLOW-UP INTERVAL 80

6 weeks = 1 2 months = 2 3 months = 3 6 months = 4 1 year = 5 Death (Ca) 6 Death (Other) 7

Fig. 4B



ST. BARTHOLOMEW'S HOSPITAL

DEPARTMENT OF UROLOGY

REGIONAL RENAL HYPOTHERMIA

1	2	3	4	5	6

SERIAL NUMBER 7 8 9 10

CARD NUMBER 11 12 — 3

AGE (years) 13 14

SEX M–1 F–2 15

INITIAL ASSESSMENT

Date — Month 16 17 — Year 18 19

1. SERUM CREATININE 20 21 22
2. CREATININE CLEARANCE in ML PER MIN. (mean of 2) 23 24 25
3. I.V.P. PARENCHYMAL VOLUME INDEX 26 27 28
4. M.S.U. 1. Sterile 2. Proteus 3. E.Coli 4. Pseudo 5. Str.F. 6. St. Albus 7. Other — 1st 29 — 2nd 30
5. METABOLIC WORK UP 1. Normal 2. Abnormal 31

OPERATION

Date ....

1. ISCHAEMIA TIME IN MINUTES 32 33 34
2. STONE CULTURE 1. Sterile 2. Proteus 3. E.Coli 4. Pseudo 5. Str.F. 6. St.Albus 7. Other — 1st 35 — 2nd 36
3. CHEMICAL ANALYSIS OF STONE 1. Ca-oxalate 2. Tri-phosphate 3. Uric Acid 4. Cystine 5. Other 37
4. BLOOD LOSS 0–500 = 1 500–1000 = 2 1000+ = 3 38
5. KIDNEY CLEARED = 1 Not cleared = 2 39
6. OTHER PROCEDURES No = 1 Yes = 2 40

POST OPERATION

1. SERUM CREATININE 41 42 43
2. CREATININE CLEARANCE (After removal of Nephrostomy tube – mean of 2) 44 45 46
3. RENACETIN VIA NEPHROSTOMY TUBE No = 1 Yes = 2 47
4. PLAIN X-RAY OF ABDOMEN Stones absent = 1 Stones Present = 2 48

WAL 94166

Fig. 5

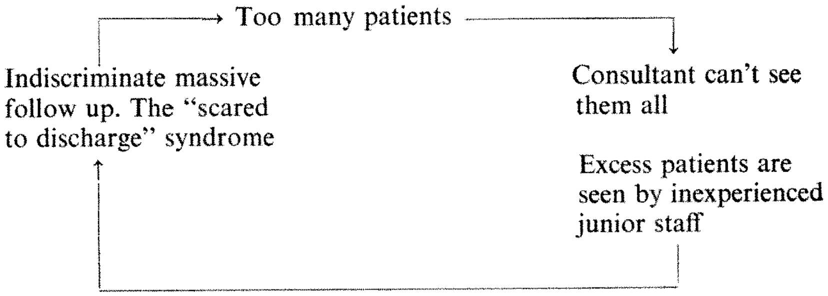

Too many patients
Consultant can't see them all
Excess patients are seen by inexperienced junior staff
Indiscriminate massive follow up. The "scared to discharge" syndrome

Fig. 6

Once this circle is broken, time becomes available to make definitive and sensible decisions which speed the patient back to the community. This may sound a harsh doctrine, but expressions of satisfaction from patients for rapid treatment and shortness of clinic waiting time coupled with lack of complaint would convince us otherwise.

2. **The ability to review performance rapidly.** One of the most worrying factors in a haphazard system of patient management is the mentally numbing situation for the consultants of not knowing reasonably accurately from day to day or from month to month either the patient numbers or the amount and type of work passing through the department. One works on an "impression" which can be entirely erroneous. For example:

(*a*) The specific number of patients being treated for any disease entity is immediately available. After the system had been running for only 6 months we found that we were seeing 3 times as many new cases of carcinoma of the bladder as both consultants "thought" were being seen.

(*b*) Likewise the interesting fact has emerged that nearly 50% of all patients by the time that they had been investigated by the Department had no demonstrable physical, radiological or pathological evidence of disease in the urinary tract, in spite of having suffered from a brief period of urological symptomatology.

(*c*) Similarly, nearly 25% of all patients presenting with haematuria had no demonstrable urological pathology.

(*d*) The system has revealed a complete change from open prostatectomy to transurethral resection for benign prostatic hypertrophy. This change coincides with the availability of the new fibre-optic endoscopic equipment.

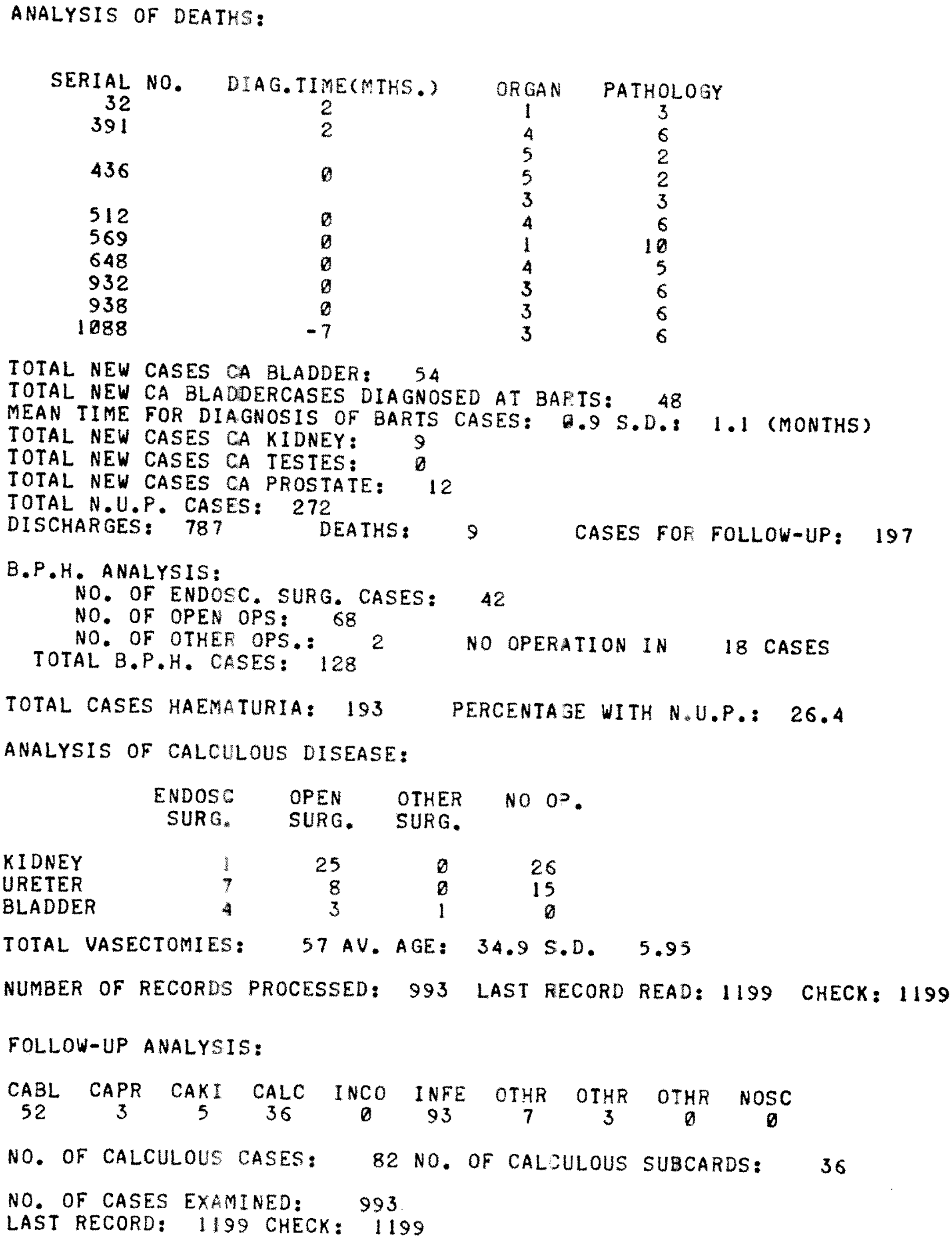
Thus with only 4 years of data processed we have already discovered areas of interest which had escaped attention.

The type of data put out by the computer from the master sheet is shown in Figure 7.

The Data available from the Sub-cards. As we had hoped, it is from the sub-card analysis that the most valuable information is obtained. A small example of the total amount of information that is readily available is shown in the sample print-out based on data obtained on patients with carcinoma of the bladder (Fig. 8).

It is possible to see exactly how many patients with each type of tumour were dealt with in 1971. We can see how each group of patients fared and responded to treatment. Comparison with future years will enable us to see trends and modify treatment regimes accordingly without need to recourse to the main hospital records.

The sub-card for regional renal hypothermia has enabled us to review quickly data on pre- and postoperative renal function and infection in patients so treated. There has been no need to withdraw the patients' main records from the hospital archives, a tedious exercise only too well



```
ANALYSIS OF DEATHS:


   SERIAL NO.   DIAG.TIME(MTHS.)    ORGAN   PATHOLOGY
       32              2              1         3
      391              2              4         6
                                      5         2
      436              0              5         2
                                      3         3
      512              0              4         6
      569              0              1        10
      648              0              4         5
      932              0              3         6
      938              0              3         6
     1088             -7              3         6

TOTAL NEW CASES CA BLADDER:   54
TOTAL NEW CA BLADDERCASES DIAGNOSED AT BARTS:   48
MEAN TIME FOR DIAGNOSIS OF BARTS CASES:  0.9 S.D.:  1.1 (MONTHS)
TOTAL NEW CASES CA KIDNEY:    9
TOTAL NEW CASES CA TESTES:    0
TOTAL NEW CASES CA PROSTATE:   12
TOTAL N.U.P. CASES:  272
DISCHARGES:  787       DEATHS:    9       CASES FOR FOLLOW-UP:  197

B.P.H. ANALYSIS:
     NO. OF ENDOSC. SURG. CASES:   42
     NO. OF OPEN OPS:   68
     NO. OF OTHER OPS.:    2      NO OPERATION IN    18 CASES
  TOTAL B.P.H. CASES:  128

TOTAL CASES HAEMATURIA:  193     PERCENTAGE WITH N.U.P.:  26.4

ANALYSIS OF CALCULOUS DISEASE:

            ENDOSC    OPEN    OTHER   NO OP.
             SURG.    SURG.   SURG.

KIDNEY          1      25       0      26
URETER          7       8       0      15
BLADDER         4       3       1       0

TOTAL VASECTOMIES:    57 AV. AGE:  34.9 S.D.   5.95

NUMBER OF RECORDS PROCESSED:  993  LAST RECORD READ: 1199  CHECK: 1199


FOLLOW-UP ANALYSIS:

CABL  CAPR  CAKI  CALC  INCO  INFE  OTHR  OTHR  OTHR  NOSC
 52     3     5    36     0    93     7     3     0     0

NO. OF CALCULOUS CASES:    82 NO. OF CALCULOUS SUBCARDS:    36

NO. OF CASES EXAMINED:    993
LAST RECORD:  1199 CHECK:  1199
```

Fig. 7

Histological Grade (Primary Tumours only)
(Number of Cases recorded: 53)

Category	*Number*	*Percentage of Total Recorded*	*Mean Age*
Benign	1	2	46
Well diff.	15	28	61
Mod. diff.	23	43	65
Poor diff.	12	23	71
Not known	2	4	65

Clinical Staging (Primary Tumours only)
(Number of Cases recorded: 53)

Category	*Number*	*Percentage of Total Recorded*	*Mean Age*
T1	23	43	58
T2	13	25	72
T3	10	19	70
T4	7	13	66

Initial Treatment of 23 T1 Cases

Category	*Number*	*Percentage of Total Recorded*
None	0	0
Endosc. diath.	20	87
Open cystodiath. or part. cyst.	2	9
Total cystect.	0	0
Radiotherapy	1	4
Other	0	0

N.B.—Figures may not balance to 23 cases or 100% owing to multiple treatments for some patients.

Subsequent Treatment of 23 T1 Cases in First Year

Category	*Number*	*Percentage of Total Recorded*
None	3	13
Endosc. diath.	19	83
Open cystodiath. or part. cyst.	1	4
Total cystect.	0	0
Radiotherapy	0	0
Other	0	0

N.B.—Figures may not balance to 23 cases or 100% owing to multiple treatments for some patients.

Fig. 8

known to many research workers who have tried to assemble meaningful retrospective clinical information. Additional prospective sub-cards are now being constructed by our nephrologist colleagues for review of patients attending our combined Stone Clinic. These sub-cards are intended to lock easily into the master card system.

UROLOGY OUT-PATIENT CLINICS

PLANS FOR BOOKING APPOINTMENTS

1. When all medical staff present, i.e. 1 Consultant
   1 Senior Registrar
   1 Junior Registrar
2. When Consultant or Senior Registrar away
3. When Junior Registrar away

Time	All medical staff present		Consultant or Senior Registrar away		Junior Registrar away	
	New Patients	Old Patients	New Patients	Old Patients	New Patients	Old Patients
2.00 p.m.	2	2	1	1	2	
2.15 p.m.	2	1	1	1	2	
2.30 p.m.	2	1	1	1	2*	
2.45 p.m.	2*	1	1*	1	1*	2
3.00 p.m.	1*	3	1*	1		3
3.15 p.m.		4		3		3
3.30 p.m.		4		3		3
3.45 p.m.		4		3		3
4.00 p.m.						
Recent ward discharges		4		3		3
Casualty referrals		4		3		3
Total	9	28	5	20	7	20
Number of FU patients (i.e. those patients making their next appointment at the time of attending a clinic)		20		14		14

* From Casualty or other parts of the hospital or Emergency.

Fig. 9

Discussion

The Organisation of the Out-patient Clinic

1. **Patient Bookings.** Arising from the computer record sheet and the definitive discharge decision, and after discussion with the Hospital's Administrative Officers, it was decided to invite the Work Study Group from the Department of Health to review the functioning of the out-patient clinic. For a period of a month, consultants, senior and junior registrars were assessed as to their ability to process both new and old patients over a timed period. Not unexpectedly, there was considerable variation in the rate at which each grade of doctor could process each category of patient. Those with more experience dealt with patients in a shorter time. On the basis of these new timings a realistic schedule of clinical bookings was made, also taking into account the changes necessitated due to the absence of doctors on holiday or when sick. This resulted in a booking plan which is shown in Figure 9.

Implementation of the computer sheet plus the booking plan resulted in a transformation of the clinic scene. The patients were now generally seen within a few minutes of their booked appointment times and the doctors had sufficient time to interview the patients. The consultants also had adequate time between cases to supervise and discuss problems with the junior staff. A large part of the success of this system has been due to the drastic curtailment of unnecessary follow-up appointments resulting from the introduction of computerised master sheets discussed above. The reduction in the number of follow-up patients is permitting us to increase the number of new patients that can be booked for the clinic and thus cut the time that new patients need to wait for an initial appointment.

2. **The Disadvantages.** The major disadvantage that has been revealed, although numerically insignificant, has been potentially serious for the individual patient affected. We have on several occasions completed our investigation of a patient and started him on appropriate treatment, and discharged him to the care of his general practitioner. It has been recommended to the patient that his treatment could be quite adequately maintained under the care of his practitioner who has been fully informed by one or more communications. Despite this fact, we have had several patients whose treatment has been allowed to lapse, who have become symptomatic and have been sent back to the Casualty Department as a new patient without re-referral to our department. Whether these events can be ascribed to the system is perhaps questionable. It may be that the system has more clearly revealed such deficiencies.

We hope that with the reorganisation of the Health Service better communication can be established between Departments such as our own and the general practitioner.

In conclusion, it seems to us that the development of similar simple systems could bring equal benefit to other departmental areas within the Hospital Service.

Summary

This paper describes the development and practical application of a computer-based record system in a urological department.

It demonstrates how such a system can provide a clinical flow sheet for day-to-day use combined with a computerised data store for both clinical evaluation and for research purposes.

The paper also outlines how the system has improved patient handling and general departmental efficiency.

We should like to acknowledge with grateful thanks the valuable help given to us by numerous members of the junior medical staff who have worked in the Department and to our secretaries and punching and computer staff whose assistance has made the system work.

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Short Case Report

Late Haemorrhage following Renal Biopsy

Bleeding following a percutaneous renal biopsy usually gives rise to symptoms within a few hours of the procedure. We describe a patient in whom haemorrhage occurred 18 days after the biopsy leading to an incorrect preoperative diagnosis.

Case Report

A man of 36 with malignant hypertension and disseminated lupus erythematosus, both of recent onset, was referred for a renal opinion (day 1). On examination, weight 60·0 kg, B.P. 230/150 lying and standing, Grade III hypertensive retinopathy. Investigations: IVP (conducted 6 weeks previously when the creatinine clearance was 55 ml/min) normal size and position of the kidneys; creatinine clearance 6 ml/min; 24-hour protein excretion 2·3 g; A.N.F. present, titre more than 1 in 320; platelet count 69,000/cu.cm; coagulation studies: normal.

The hypertension was controlled with guanethidine and intermittent parenteral diazoxide. On day 3 a left renal biopsy was performed using a Vim Silverman needle and two strips of cortex containing a total of 59 glomeruli were obtained. Histology showed changes compatible with lupus erythematosus and hypertension. Treatment was then begun with prednisolone 100 mg orally per day and azathiaprine 1 mg per kg body weight. On day 7 regular haemodialysis was started because of hyperkalaemia. On day 21, whilst in bed in the ward, after a total of 48 hours of haemodialysis, the patient collapsed with an unrecordable blood pressure and intense pain in the left lower quadrant of the abdomen. Signs of peritonitis rapidly developed, being most marked in the left lower quadrant. There was no loin swelling. Within 2 hours the blood pressure rose spontaneously to 190/120. At laparotomy a large haematoma adjacent to the lower pole of the left kidney was found and drained. There was no bleeding point and the abdominal viscera were normal. During an uneventful convalescence there were no signs of further haemorrhage. On day 45, a left nephrectomy was performed to help control the hypertension, and at this operation a further large haematoma was found around the lower pole of the left kidney.

Comment

This case is reported to emphasise the unusual cause of an abdominal catastrophe 18 days after renal biopsy. The platelet count had risen to normal with immunosuppressive treatment. The preoperative diagnosis was thought to be either a perforated duodenal ulcer or pancreatitis, both of which could have been enhanced by the high dose of prednisolone. Haemorrhage from the kidney biopsy site is a major complication of this procedure and it usually occurs within hours of the biopsy. Slotkin and Madsen (1962) and Hampers and Prager (1964) have reported single cases of post-biopsy bleeding 10 days after the procedure with an uneventful intervening period. Apparently a delay of 18 days has not been recorded.

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Acute Hypertension and Perirenal Haematoma—A New Aspect of Page's Syndrome

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Hypertension as a result of renal disease is a well-known phenomenon. It appears to be less known that perirenal processes also may cause hypertension after months and even years, probably due to constriction of the kidneys, causing renal ischaemia. Experimentally, such a mechanism was demonstrated in dogs by Page as early as 1939.

We have recently observed a patient in whom a perirenal haematoma caused acute severe hypertension. Although the phenomenon may be rare this clinical entity has great interest. In order to estimate the frequency of this complication we have reviewed the case records of the patients who underwent renal biopsies at Umeå Hospital in 1969-1972 and in whom heavy bleeding resulted from the biopsy.

Material

Case report. The patient was a 17-year-old, previously healthy, male. Because of symptoms indicating left-sided ureteral obstruction, intravenous urography was done. The urogram showed hydronephrosis due to obstruction at the ureteropelvic junction. The patient was admitted for operation. On the day of admission his blood pressure was 125/85 mm Hg. On 26th September 1972, resection of the renal pelvis and pyeloplasty by the Hynes-Anderson technique were performed. A catheter of Brandenburg (Rüsch) type was used for a nephrostomy. There were no postoperative complications until 2nd October, when the patient developed heavy haematuria through the nephrostomy catheter and from the bladder with increasing pain in the left flank. The haemoglobin value decreased from 12·1 to 8·5 g/100 ml. The patient's general condition deteriorated, tachycardia and pallor developed, which in connection with a tender mass in the operated region, indicated the presence of severe haemorrhage. Despite these findings the blood pressure was highly elevated (Fig. 1). Immediate operative exploration of the left kidney was performed and a large perirenal haematoma (about 1000 ml) was removed. A bleeding artery in the renal parenchyma at the site of the nephrostomy was ligated. As soon as the patient had been anaesthetised (thiopental sodium, N_2O and halothane) the blood pressure fell. It increased again during the first postoperative hours but soon attained a normal level (Fig. 1).

Renal Biopsy Cases

During the period 1969-1972, 390 percutaneous renal biopsies were performed at Umeå Hospital. A Franklin-Silverman needle was used and simultaneous renal angiography was performed (Junghagen *et al.*, 1968). Selective angiography was repeated immediately after the biopsy. A slight leakage of contrast medium was seen in most cases, indicating a slight perirenal bleeding from the biopsy channel. In 7 cases heavy perirenal bleeding occurred, producing a palpable mass in the kidney region and necessitating blood transfusions. In 2 of the cases surgical exploration of the kidney proved necessary. The diagnoses in 7 cases were: chronic glomerulonephritis, 1 case, chronic pyelonephritis, 2 cases, nephritis epidemica, 1 case, chronic nephropathia, not specified, 2 cases. The 7th patient, being examined for proteinuria, had on histological examination normal renal parenchyma. In this case only, the blood pressure increased after biopsy from the initial value of 130/80 to 175/95 mm Hg. It remained at this level during the next 5 days after which period it gradually returned to normal. Four of the other patients suffered from hypertension and this remained essentially unchanged after biopsy. The 2 remaining patients were normotensive and had no increase in blood pressure in association with their perirenal haematoma.

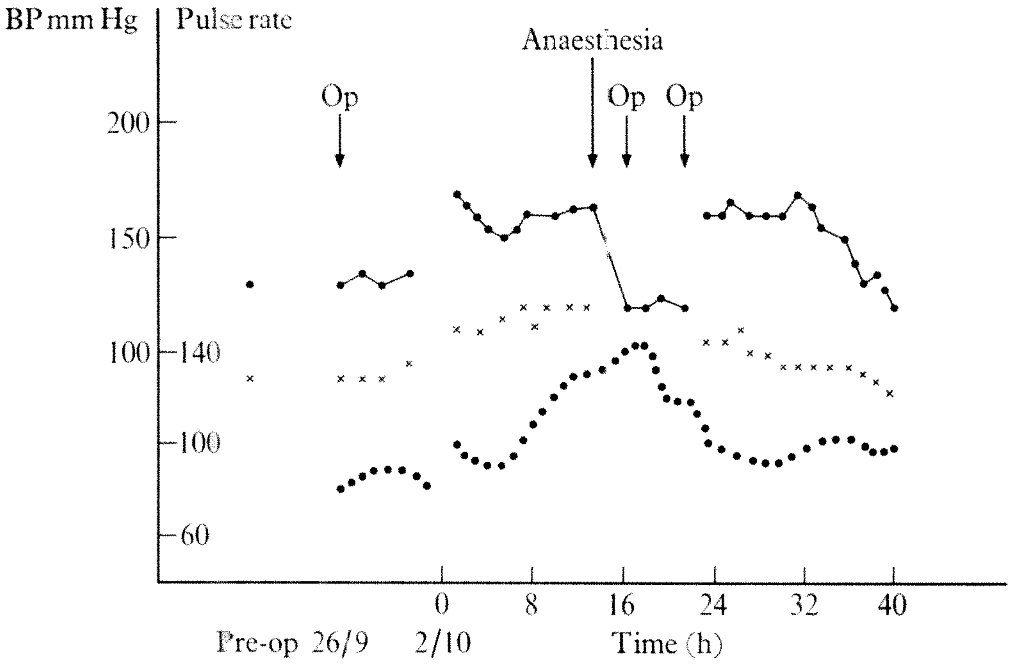

Fig. 1. Diagram illustrating variations in pulse rate (........), and blood pressure (systolic .-.-.-.-, diastolic × × × × ×) in connection with the development of a massive perirenal haematoma after uretero-pelvioplasty.

Discussion

Hypertension can be experimentally induced by constricting the renal artery of one kidney, as was first demonstrated by Goldblatt *et al.* (1934). Later, in 1939, Page produced hypertension by wrapping a kidney in Cellophane. It seems that both forms of hypertension have a denominator in common: the ischaemia of the kidney. In the first case a perinephritic shell develops which causes impaired circulation in the renal parenchyma by compressing the kidney. In the second case renal blood flow is decreased because the renal artery constriction limits the blood flow to the kidney.

Our observations suggest that perirenal processes cause rising blood pressure only if the patient does not suffer from any disease of the renal parenchyma. The patient presented in the case report as well as the patient from the renal biopsy material who developed hypertension, both had normal renal parenchyma. Two out of the 6 patients with renal disease who developed large perirenal haematomas after biopsy were normotensive before biopsy. None of them developed hypertension. The remaining 4 patients with renal disease and perirenal haematomas all had pronounced hypertension before biopsy was performed.

Great variations are observed in the plasma level of renin in different kinds of renal disease (Peart, 1971). To our knowledge, no report has been made on the renin content of renal parenchyma in different kinds of renal disease.

Although the mechanism causing hypertension in renal ischaemia is still not understood in detail, the renin-angiotensin-aldosterone system is probably involved in the process. Our material of perirenal haematomas after renal biopsy suggests that the mechanism causing hypertension in cases with normal kidneys is obviated by disease of the renal parenchyma. In such cases it is possible that the kidney has no capacity to increase its production or release of renin beyond that in the existing renal disease. This is consistent with experimental data suggesting the existence of "a close correlation between the excretory function and renin content of the kidney and probably also the renin released from it" (Gross, 1967).

In the studies made by Page constricting perinephric tissue developed in 3-5 weeks. After this time the blood pressure began to rise. If the experimental kidney was removed hypertension disappeared. Also from clinical experience (Grant *et al.*, 1971) cases have been reported of perirenal processes causing hypertension months and even years after renal trauma. Spontaneous perirenal haematoma is a rare phenomenon, although it is long known. Renal disease such as hydronephrosis or renal tumour or vascular disease such as aneurysm, haemangioma or periarteritis nodosa have been shown to be the provoking factor (Andersson *et al.*, 1970). In one case of polycythaemia vera with spontaneous perirenal haematoma described by Mackenzie as early as 1930, a moderate rise in blood pressure was observed but was not discussed more closely.[1] However, we have not found any report in the literature of cases of acute hypertension in previously healthy patients, the hypertension being caused by renal compression of a complicating post-operative perirenal haematoma.

In acute massive perirenal haematoma immediate surgery is indicated. In these cases a considerable decrease in the circulating blood volume may occur with subsequent peripheral vascular constriction and severely impaired tissue perfusion, despite the fact that the patient may have an elevated blood pressure, as in our case. It is essential to recognise this clinical entity in order to avoid delay of the operation required. The risk of development of a shock syndrome more resistant to therapy thereby can be avoided.

Summary

Chronic hypertension induced by perirenal constrictive processes is known from experimental studies as well as from clinical experience. In this report we present 2 cases of acute hypertension induced by massive perirenal haematoma, in 1 case as a complication following pyeloplasty, in the other as a complication following percutaneous renal biopsy.

Since the shock may be masked by the hypertension (and operation thereby postponed) it is essential to be aware of this syndrome.

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[1] Recently (Jameson, 1973) transient hypertension, probably of a similar genesis, was noted in 6 patients in a series of 90, admitted to hospital after closed renal trauma.

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Short Case Report

Post-traumatic Haemoglobinuria

A 25-year-old woman sustained a left back injury in an automobile accident. Despite back pain, she did not seek medical attention until 9 days after injury, when she noted "black" urine. Urinalysis showed no red blood cells but was strongly positive for haemoglobin. Urograms showed extravasation from a middle calyx (Fig. 1, A). Her gross haemoglobinuria persisted for a few days and then ceased. Urogram 8 days later was normal (Fig. 1, B).

Delayed haematuria has been seen 24 to 72 hours after renal cortical injury as a result of either delayed seepage of blood into the tubules or dislodgement of a calyceal clot (Mitchell, 1967). The injury in the present case was most likely a contained cortical haematoma and occurred in close proximity to a middle fornix. A rupture through the fornix 9 days later probably was secondary to increased pressure within the haematoma from red blood cell lysis and breakdown products of haemoglobin, as occurs with subdural haematomas (Collins *et al.*, 1969), and would explain the haemoglobinuria.

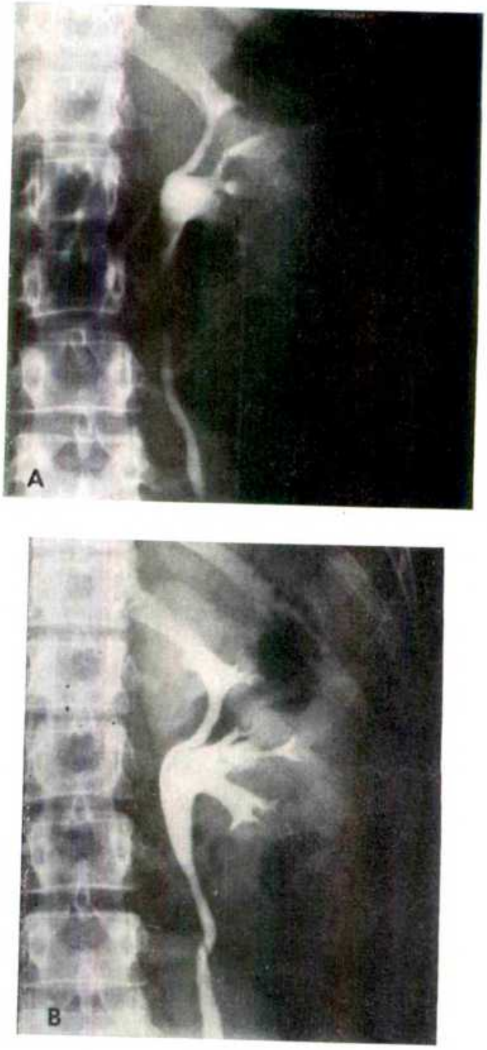

Fig. 1

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The Angiographic Evaluation of Renal Pelvic Carcinoma

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Renal pelvic carcinoma is generally considered to be a rare lesion. Riches, Griffiths and Thackray, (1951) found that among 2,314 kidney tumours, 9·5% were malignant tumours derived from the renal pelvis. However, over the last few years, a rising incidence of renal pelvic carcinoma has been noted (Grayhack, 1972). In Yugoslavia, the incidence of renal pelvic carcinoma is comparable with that of hypernephroma and seems to be related to the occurrence of the endemic nephropathy which occurs in that part of the world (Petković *et al.*, 1968). A possible association between the occurrence of renal pelvic carcinoma and analgesic abuse has recently attracted attention (Høybye and Nielsen, 1971).

The correct preoperative diagnosis of renal pelvic carcinoma is of considerable practical importance. In this article the role of angiography is considered in the diagnosis and attention is drawn to an additional angiographic sign, which has hitherto not received much attention in the literature.

Case Reports

Between 1968 and 1972, 6 cases of renal pelvic carcinoma were studied by selective renal angiography.

Case 1. A 53-year-old female presented with a history of recurrent urinary tract infection over a 5-month period and one episode of haematuria. She had for many years taken large quantities of phenacetin-containing analgesics. Her blood urea was 106 mg/100 ml and her creatinine clearance was 35 ml/min.

Excretory urography showed a small left kidney with significant cortical loss. No calyces were visualised in the lower pole of the right kidney and an irregular filling defect was present in the renal pelvis (Fig. 1). A right selective renal arteriogram showed enlargement of the pelvi-ureteric artery (Fig. 2). There was no neovascularisation. The interlobar arteries in the right lower pole showed diminished branching into arcuate and interlobular arteries. There was a marked reduction of the density of the nephrogram in the lower pole (Fig. 3).

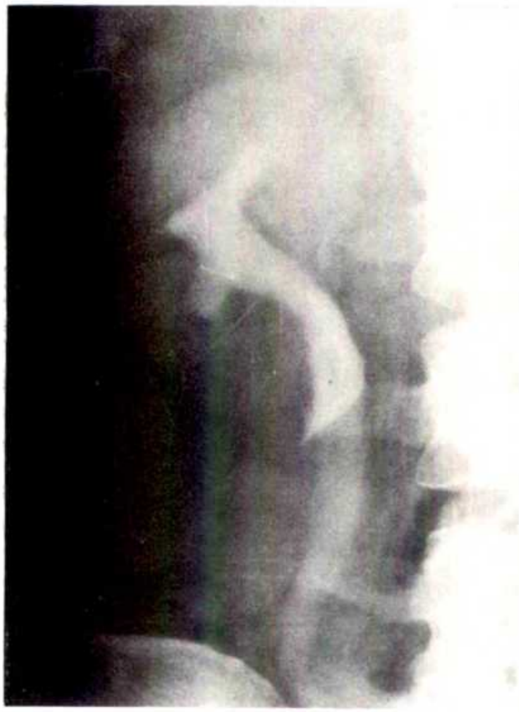
At cystoscopy, a papilliferous tumour was found in the region of the right ureteric orifice and biopsy of this revealed a poorly differentiated transitional cell carcinoma. Surgery was not undertaken because of the patient's poor general status and impaired renal function.

Case 2. A 77-year-old male complained of symptoms of prostatism. Routine excretory urography revealed an irregular filling defect in the upper part of the right renal pelvis with non-opacification of the calyces in the upper pole of the right kidney. On selective arteriography there was poor filling of arteries in the upper pole of the right kidney. A prominent superior capsular artery was noted (Fig. 4). The density of the nephrogram in the upper pole was diminished. No neovascularisation was noted.

A right nephro-ureterectomy was performed. An *in-vitro* combined arteriogram and retrograde pyelogram showed a large filling defect lying within and almost totally occupying the dilated upper pole calyces. The interlobar arteries in the upper pole showed diminished branching into arcuate and interlobular vessels (Fig. 5). A transitional cell carcinoma confined to the pelvis and upper calyces was found at histology. There was no evidence of parenchymal invasion by the tumour. However, significant dilatation of the tubules in the upper pole indicated the presence of obstruction.

Case 3. This patient, a 50-year-old male, presented with painless haematuria.

Excretory urography revealed an irregular filling defect in the right renal pelvis with no opacification of the



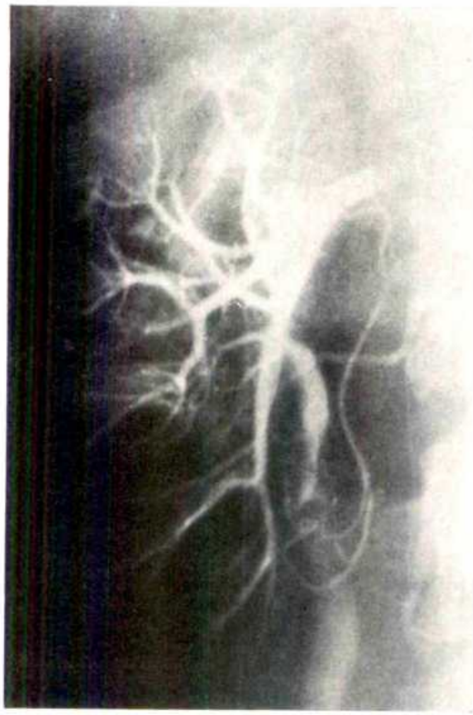


Fig. 1. Case 1. No calyces are seen in the lower pole of the kidney and there is an irregular filling defect in the renal pelvis.

Fig. 2. Case 1. There is prominence of the pelvi-ureteric artery. The interlobar arteries in the lower pole show diminished branching—the "pruned tree" appearance.

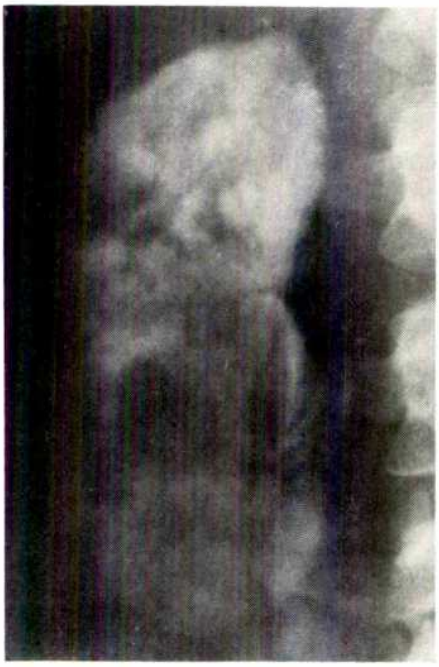
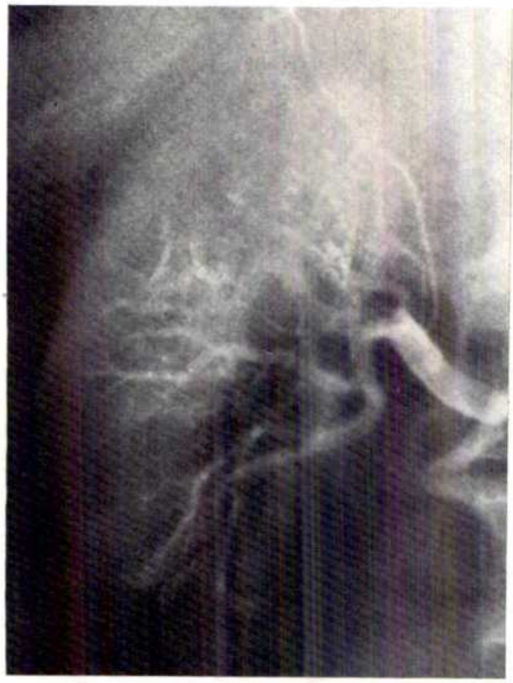


Fig. 3. Case 1. There is marked reduction in the density of the nephrogram in the lower pole.



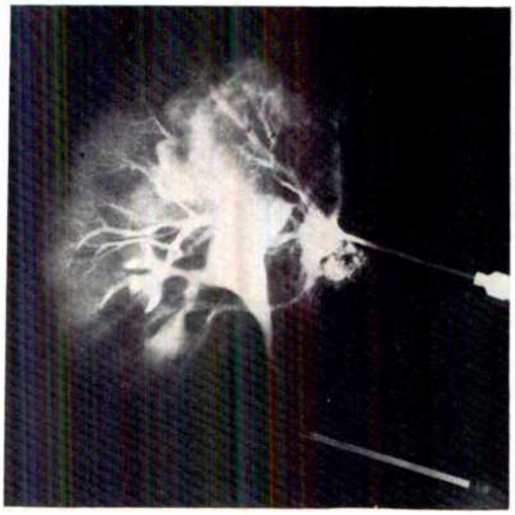


Fig. 4. Case 2. There is poor filling of arteries in the upper pole of the right kidney. A prominent superior capsular artery is present. (Screen artefacts are superimposed on the upper pole of the kidney.)

Fig. 5. Case 2. An *in-vitro* combined arteriogram and retrograde pyelogram shows a large filling defect almost totally occupying the dilated upper pole calyces. The interlobar arteries in the upper pole show diminished branching.

upper pole calyces (Fig. 6). A right selective renal arteriogram showed diminished vascularity in the upper pole with decreased branching of interlobar arteries into arcuate and interlobular arteries (Fig. 7). No neovascularisation was noted. There was a considerable reduction in nephrographic density in the upper pole.

A right nephro-ureterectomy was performed. A transitional cell carcinoma was found to be filling the upper pole calcyces and to be invading the renal parenchyma.

Case 4. A 5-month history of intermittent haematuria and pain in the right loin were the presenting symptoms of a 69-year-old female. A mass was palpable in the right iliac fossa. The blood urea was normal.

Excretory urography showed no excretion of contrast medium on the right side. The left kidney was normal. The right renal pelvis contained irregular filling defects on retrograde pyelography and the calyces could not be outlined by contrast medium (Fig. 8).

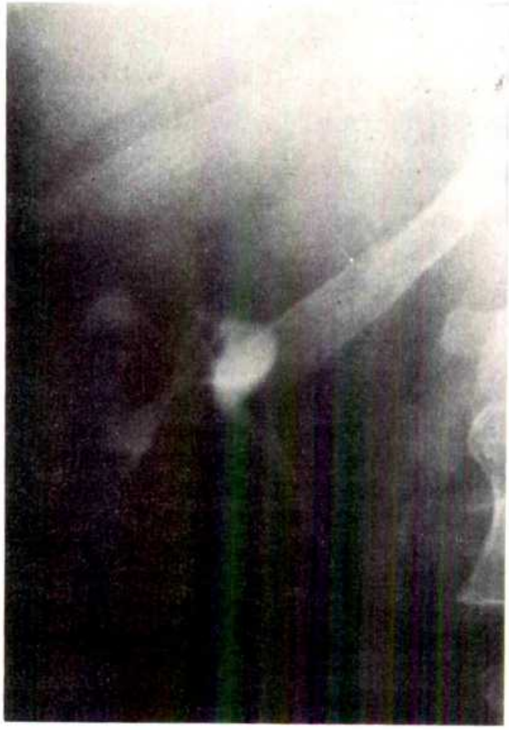
A right renal arteriogram showed no evidence of neovascularisation in the right kidney; nor was there any displacement of intrarenal arteries (Fig. 9). The interlobar arteries were uniformly attenuated with diminution in branching—the "pruned tree" appearance.

A right nephrectomy was performed. On pathological examination, the kidney was mostly replaced by tumour. There was marked perirenal spread of the tumour with invasion of the pelvis, proximal ureter and hilar vessels. Histology revealed an anaplastic transitional cell carcinoma with extensive destruction and invasion of renal parenchyma.

Case 5. A 65-year-old female, presented with painless haematuria and backache. There was no history of analgesic intake.

On excretory urography, an irregular filling defect was present in the left renal pelvis. There was also irregular destruction of the left upper pole calyces (Fig. 10). A left selective renal arteriogram showed no abnormality (Fig. 11).

A left nephro-ureterectomy was carried out. A transitional cell carcinoma of the renal pelvis was present without any parenchymal invasion.



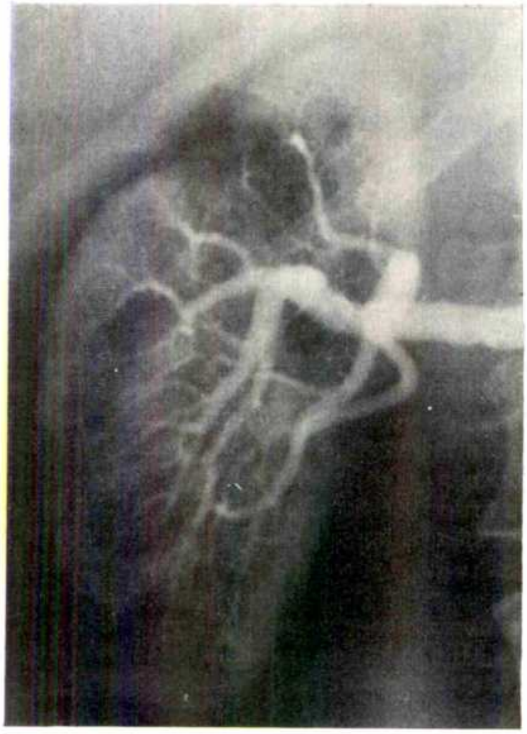


Fig. 6. Case 3. There is an irregular filling defect in the right renal pelvis with no opacification of the upper pole calyces.

Fig. 7. Case 3. There is decreased branching of the interlobar arteries in the upper pole—the "pruned tree" appearance.

Case 6. Three years prior to this admission, a 71-year-old male had a right nephro-ureterectomy and partial cystectomy for transitional cell carcinoma. He presented on this occasion with burning on micturition, increased frequency and urgency incontinence.

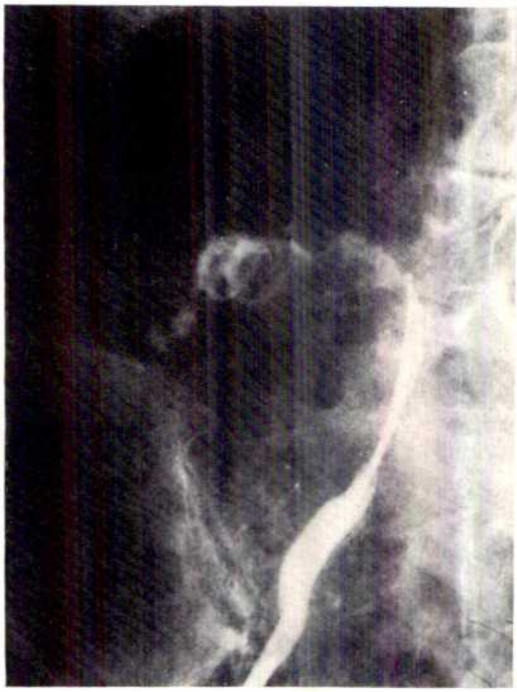
Excretory urography and retrograde pyelography revealed an irregular filling defect in one of the lower pole calyces. A left selective renal arteriogram was normal.

Recurrent transitional cell carcinoma of the bladder was confirmed by cystoscopy and biopsy. No further investigation or treatment of the renal lesion was undertaken.

Results

6 cases of transitional cell carcinoma of the kidney are presented. The diagnosis was confirmed by histological examination of the resected kidney in 4 cases. In the other 2 cases, the diagnosis was strongly suggested by the radiological appearances and by the presence of histologically proven associated transitional cell carcinoma of the bladder.

In cases 1, 2 and 3, routine urography revealed an irregular filling defect in the renal pelvis with non-visualisation of calyces in the affected part of the kidney. Definite urographic distinction between hypernephroma with invasion of the collecting system and renal pelvic carcinoma was not possible. Case 4 showed no excretion of contrast by the affected kidney on excretory urography, but retrograde pyelography revealed intrapelvic filling defects with no filling of the calyces. The appearances were considered consistent with a variety of possibilities including renal pelvic carcinoma, hypernephroma and xantho-granulomatous pyelonephritis. Cases 5 and 6 showed smaller, less extensive lesions, the urographic appearances being suggestive of transitional cell carcinoma.



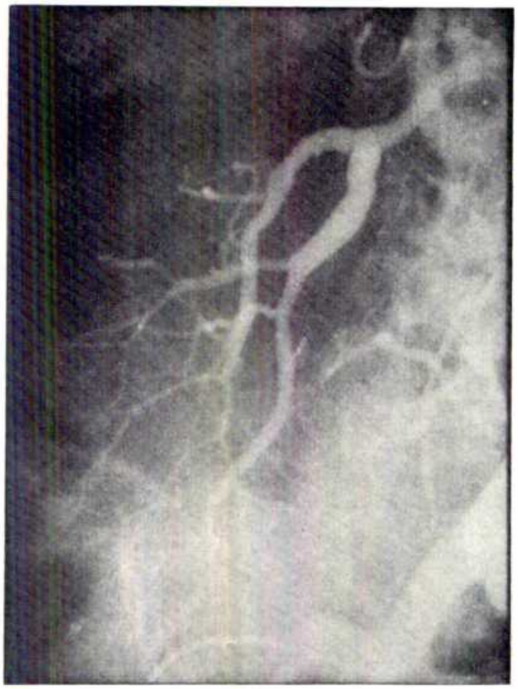
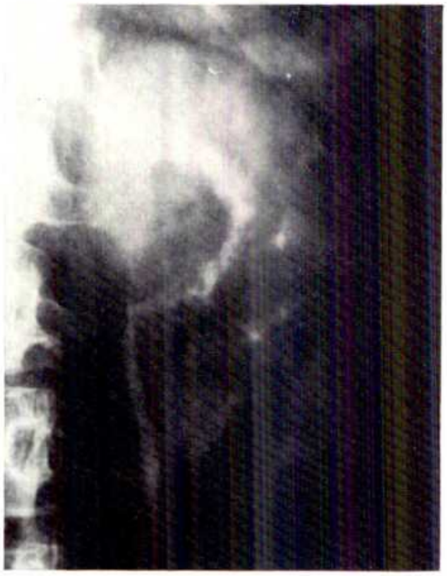


Fig. 8. Case 4. A retrograde pyelogram shows the right renal pelvis to contain irregular filling defects. The calyces could not be outlined with contrast medium.

Fig. 9. Case 4. The interlobar arteries in the right kidney are uniformly attenuated with diminution in branching—the "pruned tree" appearance.



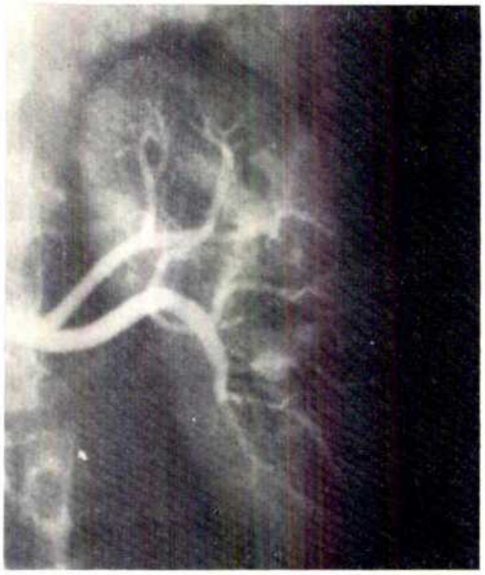


Fig. 10. Case 5. An irregular filling defect is present in the left renal pelvis with tumour extension into the upper major calyx.

Fig. 11. Case 5. The renal arteriogram is normal.

Table

Summary of Angiographic Findings in 6 Cases of Renal Pelvic Carcinoma

Prominent pelvi-ureteric artery	1
Pruned-tree appearance	4
Deficiency in nephrogram	3
Neovascularity	0
Blush	0
Vessel encasement	0
Arteriovenous shunting	0
Vascular displacement	0

The arteriographic findings are listed in Table. The arteriogram was abnormal in 4 cases. All of these cases showed a diminished branching of vessels—the "pruned-tree" appearance. In cases 1, 2 and 3, this appearance was localised to the kidney segment related to the pelvi-calyceal tumour and was associated with a breach in the nephrogram. In case 4 there was generalised diminution of arterial branching. A prominent pelvi-ureteric artery was found in 1 case. 2 patients (cases 5 and 6) with small lesions had normal arteriograms.

Discussion

The arteriographic findings in renal pelvic carcinoma have been described by various authors (Boijsen and Folin, 1961; Mitty, Baron and Felles, 1969; Schapira and Mitty, 1971; Haleem, Sprayregen and Siegelman, 1972; Rabinowitz *et al.*, 1972). However, arteriography has not been widely used in the investigation of this lesion.

A prominent arteriographic finding in 4 of the presented cases was that of diminished branching of arteries, the so-called "pruned-tree" appearance. Where the entire kidney was invaded, as in case 4, this appearance was generalised. In cases 1, 2 and 3, the "pruned-tree" appearance was limited to the kidney segment related to the pelvi-calyceal tumour. These 3 cases showed a marked reduction in the density of the nephrogram in the same segment. The possible aetiology of these appearances is of some interest. Of the 4 cases shown to have the "pruned-tree" appearance, 2 are known to have had parenchymal invasion by tumour. However, case 2 showed the appearance in the presence of a large tumour confined completely to the collecting system. Histologically, in the latter case, there was obstruction and dilatation of the renal tubules in the affected kidney segment. It is therefore likely that the "pruned-tree" appearance may be due in some instances to tubular obstruction and interstitial oedema and that it may occur even in the absence of parenchymal invasion by the tumour. In such instances there would be a diminution in the blood flow through the obstructed segment of the kidney, which would account for the segmental deficiency of the nephrogram in relation to the tumour. Thus, while the "pruned-tree" appearance and segmental reduction in nephrographic density will frequently occur with parenchymal invasion by tumour, these signs do not always indicate invasion nor are they necessarily co-extensive with the tumour.

Neovascularisation was not seen in this series in contrast to the findings of Boijsen and Folin (1961), Haleem *et al.* (1972) and Rabinowitz *et al.* (1972). Our findings were more in keeping with those of Mitty *et al.* (1969), who also found hypovascularity in the area of the tumour to be a prominent feature. A prominent pelvic artery was an important diagnostic feature in some studies (Mitty *et al.*, 1969; Haleem *et al.*, 1972; Rabinowitz *et al.*, 1972).

The renal arteriographic findings in extensive renal pelvic carcinoma are different from those in hypernephroma, which is generally a highly vascular tumour.The preoperative distinction between these entities is of great importance in treatment planning. Patients with hypernephroma may benefit from preoperative radiotherapy and subsequent radical nephrectomy, whereas transitional cell carcinoma of the renal collecting system is conventionally treated by nephroureterectomy and removal of a cuff of bladder. Arteriography is thus of particular value when urographic distinction between the two entities is not possible. On the other hand, in the presence of small transitional cell carcinomas confined to the renal pelvis or a major calyx, arteriography is unlikely to provide any additional information.

Summary

The angiographic findings are described in 6 cases of renal pelvic carcinoma.

An angiographic finding which has not hitherto been emphasised is a diminished branching of arteries in the kidney segment related to the pelvi-calyceal tumour—the "pruned-tree" appearance. This is generally associated with a deficiency of the nephrogram in the same segment. These appearances may be due to invasion of the renal parenchyma by tumour.

However, the findings may occur also in the absence of parenchymal invasion by the tumour and therefore do not necessarily reflect the stage of the disease.

We wish to thank Miss H. Rissik for the preparation of the prints and Mrs J. Atkinson for the typing of the manuscript.

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Short Case Report

An Unusual Complication of Calyceal Diverticulum

Case Report

A girl was investigated for day and night urinary incontinence at the age of 4 years. An intravenous pyelogram showed a calyceal diverticulum in the right kidney (Fig. 1), and a micturating cystogram showed vesico-ureteric reflux on the same side. Further intravenous pyelograms at the ages of 7 and 8 years showed no change in the diverticulum but the reflux was never again demonstrated. At the age of 12 she became ill with fever and a palpable mass in the right loin. This was due to a large cyst in the upper pole of the right kidney, apparently at the site of the previously noted calyceal diverticulum (Fig. 2). It is surmised that the diverticulum became sealed off and converted into a cyst. Partial nephrectomy was performed.

Comment

Calyceal diverticulum is a rare but well recognised entity (Lister and Singh, 1973). It is sometimes dismissed as an abnormality of no significance but of 54 cases reviewed by Keller, Bettex and Kuffer, 24 came to operation, most of these because of symptoms related to urinary infection or stone formation in the diverticulum.

The complication described here, mainly conversion of diverticulum to sealed-off cyst, would seem to be unusual as no similar case has been found in the literature.

It is presented as further evidence that calyceal diverticulum is not a negligible condition.

Acknowledgements

I would like to thank Mr D. M. Forrest, F.R.C.S., and Dr F. Starer for permission to publish the case.

John L. Nicholas
The Westminster Children's Hospital, London S.W.1, and Queen Mary's Hospital for Sick Children, Carshalton, Surrey.

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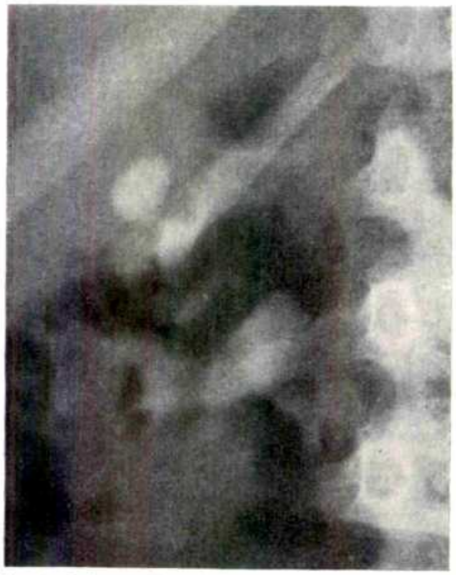

Fig. 1. Calyceal diverticulum at the age of 4 years.

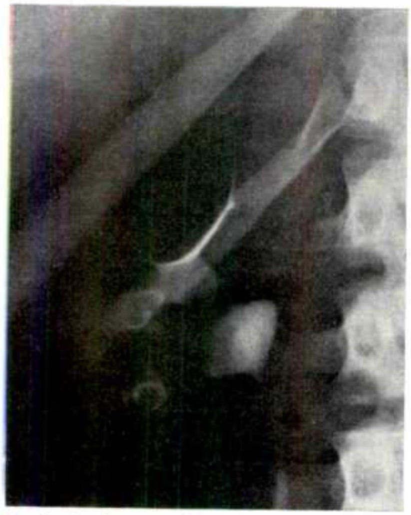

Fig. 2. At 12 years, diverticulum replaced by a large closed-off cyst.

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The Management of Urinary Fistulae following Cadaveric Renal Transplantation

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Introduction

A major surgical problem associated particularly with cadaveric renal transplantation is the development of a urinary fistula. From various published series (Hume *et al.*, 1966; Starzl *et al.*, 1970) the frequency is of the order of 10%. Similar leaks in ordinary urological practice are not associated with the dangers to which an immune suppressed patient is exposed. Not infrequently the fistulous track becomes infected with bacteria or fungi; this may be followed by septicaemia and, furthermore, the track shows little tendency to heal. The mortality from this complication is high, ranging in published series from 18 to 39% (McKinnon *et al.*, 1968; Palmer *et al.*, 1969; Starzl *et al.*, 1970; Williams *et al.*, 1970; Robson and Calne, 1971; Rees, 1972). This is particularly so since urinary leaks may be associated with tissue rejection and attempts to control this by increasing the dose of immuno-suppressive drugs, including prednisolone, make control of infection difficult and slow the rate of wound healing.

Many procedures have been tried with varied results. This paper presents our experience in treating such fistulae. The first case illustrates the kind of difficulties faced hitherto. The remaining 6 consecutive cases show that by modifying a well-described urological technique to allow for the special circumstances (Zimskind, Fettes and Wilkerson, 1967; Marmar, 1970; Schmitz, Lenz and Miridies, 1970; Orikasa *et al.*, 1973) this condition can be successfully treated. Calyceal leaks may be treated by the same technique as might have been expected from the successful treatment by a similar method reported by Fox and Tottenham (1972).

Patients

No. 1. A 30-year-old man, following bilateral nephrectomy for chronic glomerulonephritis, renal failure and severe hypertension, received a cadaver renal transplant on 1.1.67.

The donor ureter was anastomosed end-to-end to that of the recipient and this anastomosis was splinted with a large ureteric catheter brought out to the abdominal wall through the bladder. Adequate renal function was delayed by tubular necrosis. The splint was removed after 10 days. On the 16th postoperative day urine was coming from the wound, which was then explored. The ureteric anastomosis had broken down and it appeared that a short length of host ureter was necrotic. Reanastomosis was performed and a nephrostomy tube, with a separate accompanying ureteric splint, brought through the renal substance out to the surface through a stab incision. After removal of the splint and nephrostomy tube 3 weeks later the ureter became repeatedly blocked with candida albicans, in spite of appropriate antibiotics. Some urinary leakage from the site of ureteric suture persisted throughout and transplant nephrectomy was performed on 13.3.68 to remove a persistent site of serious infection. In spite of this, other complications followed and the patient died.

No. 2. A 33-year-old man underwent a cadaveric renal transplant in August 1968. The graft failed to function satisfactorily and was removed.

A second cadaver transplant was done in July 1969 with immediate function. At the time the graft was noted to have a small upper pole vessel which had been divided flush with the kidney during the donor nephrectomy.

On the 15th postoperative day he became febrile and his wound was tender. On this evidence the wound was explored. Urine was found to be leaking through the upper pole of the kidney at the site of a small area of infarction. A tube with many holes in it was inserted through the infarcted area into an upper major calyx and thence down into the ureter and bladder. The other end was brought to the skin surface as a nephrostomy. This tube was left *in situ* for 6 weeks. When removed, the wound healed with virtually no urinary leakage.

No. 3. A 52-year-old woman had a cadaver renal transplant for chronic glomerulonephritis performed on 7.4.70. Unfortunately, the donor ureter had been partially transected 5 cm below the pelvi-ureteric junction. As there was insufficient length to implant the ureter above the defect, this was repaired prior to uretero-neocystotomy. The blood supply of the lower ureter appeared adequate.

On 21.4.70 she developed a urinary fistula. At operation the leak was found at the site of the incision in the ureter. The edges were trimmed and the wound repaired over a fine catheter splint which was then brought out suprapubically through the bladder. The leak recurred from the same site on 26.4.70. A nephrostomy using Redivac plastic tubing was performed, placing the tube through the kidney across the ureteric defect and down into the bladder. This plastic tube gradually blocked with phosphatic deposits and attempts to syringe it out were unsuccessful.

On 29.5.70 the plastic nephrostomy tube was replaced with silastic tubing by railroading it through the kidney and ureter into the bladder. The plastic tube, with the silastic attached to its upper end, was withdrawn from the bladder with Lowsley's biopsy forceps. On 10.7.70 the nephrostomy tube was removed. There was no recurrence of the leak and renal function has remained excellent.

No. 4. A 19-year-old man underwent cadaveric renal transplantation and bilateral nephroureterectomy for renal failure due to chronic pyelonephritis in May 1970. The donor ureter was implanted obliquely into the bladder.

8 days later a urinary fistula developed which was thought to be originating from the stump of the nephroureterectomy but at operation it could not be demonstrated and the wound was drained and a catheter placed in the bladder. The fistula persisted. His renal function deteriorated and a retrograde pyelogram revealed a partially obstructed ureter 4 cm from the bladder with seepage above this point.

At operation the obstruction was found to be due to a band which was divided, and the ureter mobilised. A plastic tube was brought out through the abdominal wall, as a nephrostomy, its lower end lying free in the bladder. This splint catheter became blocked and a silastic tube was substituted by extracting the original splint through the urethra and bladder with a Lowsley forceps and at the same time railroading the new silastic tube into position from above. The replacement splint nephrostomy tubes were removed after 6 weeks with healing of the track and no recurrence of the ureteric obstruction.

No. 5. A male aged 37 received a cadaveric renal transplant in 1972 for end stage glomerulonephritis. The graft was rejected and removed. A second cadaveric transplant was performed but failed to function immediately. Fever and suprapubic tenderness were noted by the 3rd postoperative day and a cystogram showed extravasation of urine from the ureteroneocystotomy site. The wound was explored and the lower end of the ureter was found to be necrotic. The recipient's ureter, which was still *in situ*, was then anastomosed to the renal pelvis of the graft but the anastomosis was not splinted.

Postoperatively the patient developed meningitis and a candida urinary tract infection and unfortunately a further urinary leak occurred. The wound was again explored and the anastomosis was found to have dehisced. This anastomosis was again sutured and splinted with a latex tube passed down the ureter into the bladder. The tube was brought out through the kidney to the surface as a nephrostomy. This tube tended to become obstructed and was replaced with a silastic tube. The latter was removed 6 weeks later with permanent healing of the anastomosis and good renal function.

No. 6. A 34-year-old man received a cadaver renal transplant after bilateral nephrectomy for severe hypertension with renal failure. Renal function was immediate, but urine output declined gradually over the next few days. Graft tenderness and a further decline in urine flow prompted investigation. Cystoscopy, renography and arteriography failed to show the cause and on the 8th post-transplant day the graft was explored and a necrotic lower end of grafted ureter was found. The ureter was reimplanted but a large scrotal swelling developed in the next 48 hours. A cystogram suggested there might be a small leak from the bladder suture line, but when the wound was again explored the true site of extravasation was demonstrated by injecting indigo carmine into the ureter. It proved to be close to the site of implantation into the bladder. As the ureter was already short, reimplantation was not possible and a silastic tube with multiple side holes was passed through the skin, kidney, renal pelvis and ureter into the bladder. This was drained into a urine bag for 6 weeks. When the silastic tube was removed the track healed in a couple of days.

No. 7. A male aged 26 treated initially by haemodialysis for chronic renal failure received a cadaveric renal transplant. On the 5th postoperative day there was evidence of a urinary leak which was shown by cystography to be coming from the site of the uretero-neocystotomy. A simple uretero-vesical reanastomosis was done by spatulating the lower end of the ureter. At the time the ureter was seen to bleed where it was divided. 6 days later, after further urinary leakage, the wound was re-explored, the cystotomy incision then being suspected as the site of the leak. This was resutured after excision of its edges. At this time the viability of the ureter was questioned.

On the 12th postoperative day a third exploration was carried out as urine was still coming from the wound drain. The grafted ureter was clearly necrotic and had to be removed. The patient's own ureter was then joined to the graft just below the pelviureteric junction over a silastic splint which was passed into the bladder. The other end of the tube was brought out through the kidney as a nephrostomy. The splint was taken out after 6 weeks and there was no subsequent urinary leakage.

Discussion of Current Method

We described the management of 6 patients with ureteric fistulae following cadaver transplantation and of 1 patient with a calyceal leak. The relative success of our technique is ascribed firstly to an aggressive approach to urinary fistulae. In our experience a urinary fistula should be investigated and treated as a matter of urgency. Delay is associated with fungal and bacterial infection within the kidney and in the pelvic tissues. The initial problem is to ascertain whether fluid leaking through the wound or through a drain is urine or from a lymphatic collection. This is readily solved by measuring the urea content of the fluid particularly after dialysis. The development of a leak can even be suspected before urine appears in the wound by the presence of fever and a rise in blood urea without other signs of tissue rejection.

The site of leak is next ascertained by passing a catheter to perform a cystogram. To demonstrate a bladder leak, controlled filling of the bladder with up to 300 ml of contrast may be necessary. If no leak is seen, and renal function is good enough, we have next obtained an intravenous pyelogram or, failing that, a cone-tipped retrograde catheterisation of the transplanted ureter is attempted. This has not always proved easy or diagnostic and in these circumstances the wound is explored forthwith.

At operation the viability of the kidney and ureter is assessed from their appearance and both structures inspected for leaks. These are not always obvious and a dilute solution of indigo carmine has then been run into the bladder. If no leak is found there, the same solution is introduced into the renal pelvis with a very fine needle. We have found that the blue colour shows up the site of the fistula by staining damaged tissues as well as by the appearance of the coloured liquid through the hole.

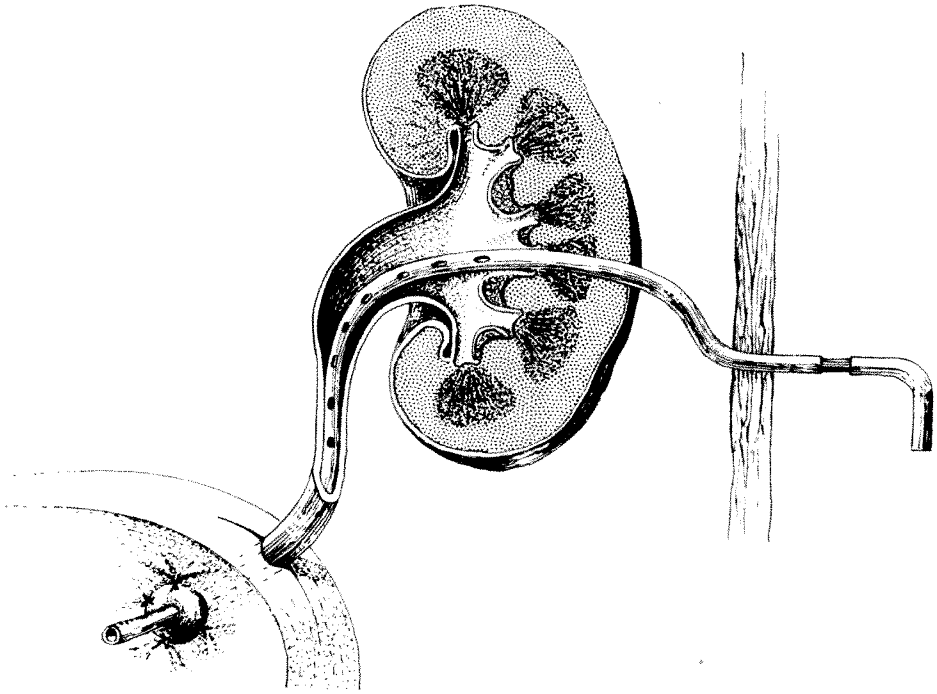

Fig. 1. Diagram of the positioning of the silastic splint tube.

If the ureteric fistula is close to the bladder and an adequate length of ureter is present, it is our practice to reinsert the ureter into the bladder through a tunnel. If, however, there is doubt about the viability of the implanted ureter, it is resected and the patient's own ureter employed as a conduit to the donor renal pelvis. Small fistulae are repaired but in all cases a silastic tube splint is used. This is positioned if necessary by making a small incision in the renal pelvis, and one end of the tube is pushed through to the bladder and the other brought out through the kidney as a nephrostomy to the surface. Many side holes are made in the silastic tubing (Fig. 1), which is left *in situ* for not less than 6 weeks when X-rays are taken to confirm the healing of the fistula. The tube is then withdrawn and healing of the nephrostomy site has never taken longer than a few days after that.

Superficially our technique resembles the Davis splint operation for hydronephrosis and we believe its success lies in using a large enough silastic tube usually 3 to 4 mm in diameter to make a fairly firm fit in the ureter, so much so that on occasions where the patient's own ureter has been used, it has been necessary to pass a ureteric catheter cystoscopically to which the splint tube is then stitched in order to draw it down through a tight vesicoureteric junction.

If postoperatively drainage through the silastic tube should become obstructed, it is comparatively simple to railroad a replacement into position by seizing the lower end of the silastic tubing in the bladder with Lowsley forceps and withdrawing it through the urethra. It is important to ensure that the silastic tube remains clear throughout the 6 weeks. We have noted that initially nearly all the urine comes from the nephrostomy and that with the passage of time more urine is passed from the bladder. It is our experience that the type of tube is important for silastic does not encrust readily. We also believe that there is a minimum time before the fistula closes or that a suture line heals firmly in these immune suppressed patients.

We attribute the failure of others to not leaving the splint tube *in situ* for a long enough period. It is of course necessary to drain the pelvic tissues separately with intermittent suction drainage to avoid any collection of fluid which could become infected Continuous suction seems to encourage fistula persistence. The same technique has proved equally effective for a calyceal fistula, the silastic tube used being brought out through the necrotic kidney tissue.

Conclusion

The adoption of sound urological principles modified to the special situation of immune suppressed patients will result in the healing of vesicoureteric, ureteric and calyceal fistulae in transplant patients. In the light of the success of this technique we have not found it necessary to adopt such radical methods as ileal conduits (O'Donoghue, Chisholm and Shackman, 1971, 1973), nor the introduction of a permanent nephrostomy with all the hazards of severe infection which this must entail.

Summary

Vesicoureteric, ureteric and calyceal fistulae in cadaver transplants may be successfully treated by early exploration and nephrostomy splintage with silastic tubing for a period of not less than 6 weeks.

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Since the preparation of this paper, one further patient has been treated successfully by this method.

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Short Case Report

Malakoplakia of Kidney and Bladder with Large Bowel Invasion

A woman aged 46 gave a 2-week history of sharp, left loin pain which radiated to her buttock. She had noted a mass in the left loin, and complained of anorexia. She had no urinary symptoms. On examination she had a firm, tender, ballottable mass in the left loin. Chest X-ray showed old T.B. Haemoglobin 10 G%, WCC 16,000, platelets 1,355,000, ESR 112. Midstream urine showed *E. coli* urinary tract infection, treated with Ampicillin. Urinary cytology, urine and sputum A.F.B. cultures were all negative. Mantoux test negative.

IVP showed normal right kidney, non-functioning left kidney, with no evidence of calculus. Cystoscopy—numerous small, raised, flat, yellowish plaques in the bladder: biopsy reported as malakoplakia, with foamy histiocytes, lymphocytes, plasma cells and calcospherules. (The bodies stained for iron and calcium, and were Michaelis-Gutmann bodies of malakoplakia.) Left retrograde pyelogram showed cut-off below the pelvi-ureteric junction, suggestive of radiolucent calculus impaction. She was thought to have hydro-pyo-nephrosis, but because of the mass neoplasm could not be excluded. Renal arteriogram—normal right kidney; selective angiogram of left kidney showed changes of hydronephrosis from distal obstruction.

Clinically the lesion appeared to be a neoplasm so exploration was undertaken. She had a large perinephric abscess which was drained. The left kidney was adherent to psoas, peritoneum and large bowel. The whole mass was resected and an end-to-end anastomosis of descending colon performed. Kidney, colon and psoas muscle all were reported as being involved with malakoplakia (see Fig.). Postoperatively she was discharged after an uneventful recovery. Follow-up at 3 and 12 months showed the bladder lesions had completely regressed.

Comment

This appears to be the first case of malakoplakia of bladder and kidney with invasion of the bowel that has been reported.

The disease is a peculiar type of chronic inflammatory reaction and non-neoplastic. *E. coli* appears to be the most likely aetiologic agent. The bladder lesions regressed spontaneously following removal of the affected kidney.

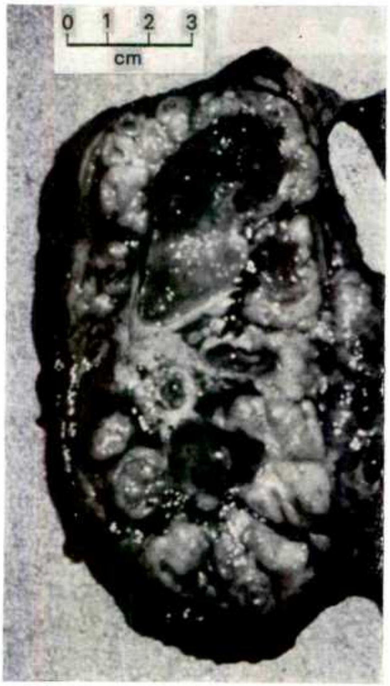

Fig. Cut surface of bisected kidney.

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Requests for reprints to E. I. Korbel.

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Some Observations and Theories on the Wide Ureter and Hydronephrosis

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Introduction

A major part of the work of the urologist is assessing and treating congenital abnormalities of the urinary tract. Amongst these, non-refluxing wide ureters and hydronephroses are common and yet the mechanisms of both dilatation and obstruction in these two conditions are ill understood. This is not because experimental work has been lacking as much research has been published on both conditions, but a simple and plausible explanation has not emerged for either situation.

An attempt is made here to simplify the classification of the wide ureter and to offer an explanation for poor emptying of both the wide ureter and the hydronephrosis.

The Wide Ureter

Classification

Needless confusion exists concerning the wide ureter because of the lack of a simple and effective classification. The term "wide ureter" is preferable to "dilated ureter", "megaureter" or "hydroureter" as it is strictly descriptive with no functional connotations. "Dilated" suggests that the ureter was once normal, which is often not the case. "Hydroureter" to some may imply a ureter under pressure, but this is far from always true. The term "megaureter" is confusing as it is often loosely applied to both refluxing and non-refluxing, obstructed and non-obstructed ureters or it may at times be reserved for the wide, non-refluxing system which is also obstructed.

The classification suggested here is based on two elementary criteria. The first and most important is whether or not there is vesicoureteric reflux and the second is whether or not the dilatation is secondary to bladder outflow obstruction. This classification (Fig. 1) has the

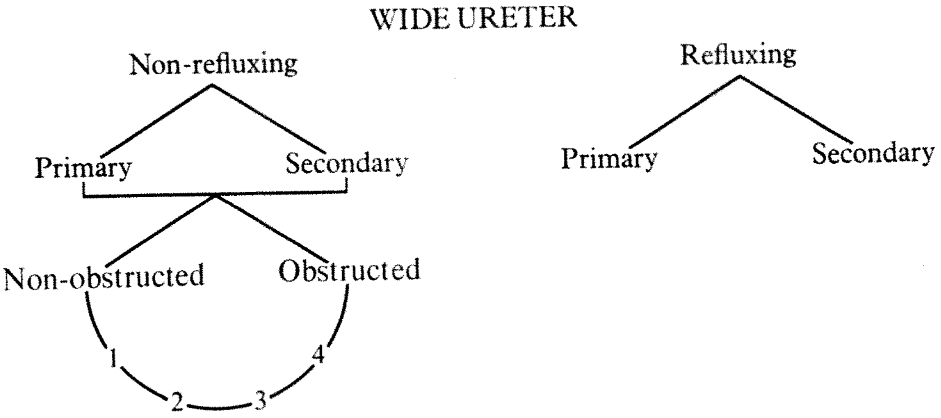
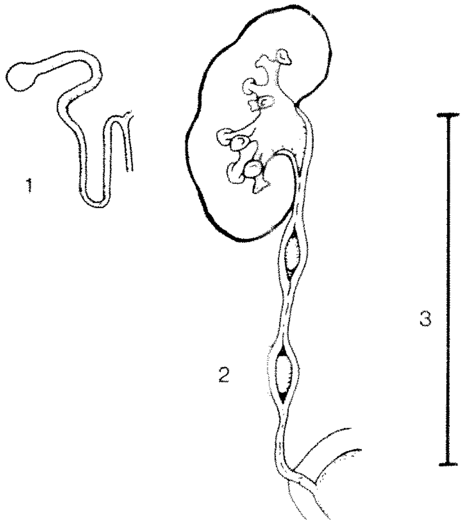


Fig. 1. Classification of wide ureters.



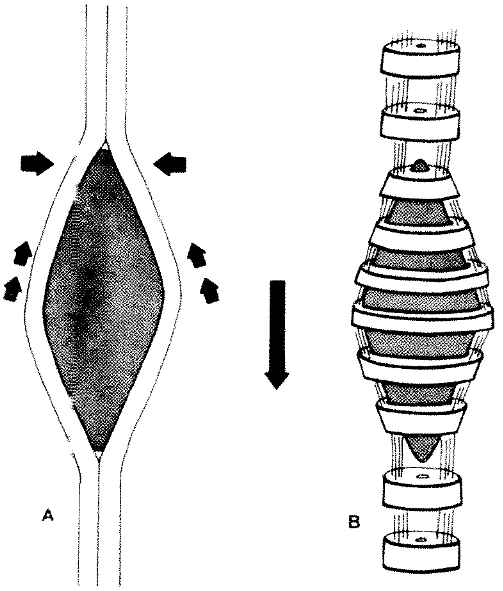


Fig. 2. The three factors influencing drainage of the renal pelvis and ureter. (1) Nephron excretion pressure. (2) Peristalsis. (3) Hydrostatic pressure or gravity.

Fig. 3. Normal ureteral peristalsis. A, Resolution of forces of circular and longitudinal muscle action on a bolus. B, Diagrammatic representation of muscle action.

advantage of being simple and broadly indicating the aetiology of the defect. Thus on the refluxing side there may be a primary defect in the ureterovesical junction or a secondary distortion from bladder neck obstruction.

The opposite of "refluxing" is not, as is commonly supposed, "obstructive"; it is "non-refluxing". It is often not fully appreciated that there is a group of wide ureters which neither allow reflux nor are they obstructed. This is a difficult concept because we have engrained in us the idea that the wide ureter is wide because it is obstructed. This is clearly not so, not only in reference to the wide dysplastic ureter which is seen in such specific congenital anomalies as the Prune Belly syndrome or the megaureter-megacystis syndrome but also as an isolated ureteric finding which is frequently unilateral.

The radiographic findings, if not analysed carefully, may suggest obstruction and it is only with the aid of dynamic studies that obstruction can definitely be excluded.

At the other end of the scale of these wide non-refluxing ureters there are, indeed, many definitely obstructed systems. Urographically there is a delay in the appearance and disappearance of the contrast medium and dynamically it is a simple matter to demonstrate a higher than normal pressure above the obstruction during a diuresis or perfusion. Although there may be a degree of dysplasia in these markedly obstructed systems, the prime defect lies in the ureterovesical junction.

Between these two extremes of obvious obstruction and non-obstruction there lies a whole range of ureters with varying degrees of obstruction. The aetiology of the dilatation and obstruction is probably a combination of abnormalities of the ureteric wall and of the ureterovesical junction and this is discussed below.

The Implications of Obstruction

In assessing the degree of obstruction and deciding whether treatment is necessary it must be remembered that what finally matters most is the effect of obstruction on the kidney. In the absence of infection it is not unreasonable to assume that a period of continuous or intermittent high pressure leads to a deterioration of renal function.

Obstruction, as referable to the upper urinary tract, implies that there is a narrowing so that the usual flow is reduced or only maintained at the cost of a higher than normal pressure within the renal pelvis and hence as a back pressure on the renal parenchyma. The pressure is generated by a combination of glomerular filtration and tubular excretion—two systems which cannot work efficiently in the presence of a high back-pressure so that the production of pressure is self-limiting. As renal impairment progresses there is a tendency for the kidneys to produce a greater volume of more dilute urine. This higher flow rate in the presence of a fixed degree of obstruction will in itself demand a higher pressure to overcome the obstruction and the problem is compounded.

A urodynamic approach is clearly the most logical means of diagnosing obstruction.

The Mechanisms of Fluid Transport in the Normal Ureter

There are 3 forces which act on the urine in the renal pelvis and encourage its transport into the bladder (Fig. 2). Firstly, there is the pressure produced by the nephron (glomerular filtration and tubular excretion): secondly, there is peristalsis; and thirdly, hydrostatic pressure (gravity).

The role each of these factors plays in transport is dependent on the circumstances which prevail at the time. Whilst lying in bed with an empty bladder, for instance, there is no hydrostatic pressure and the renal excretion pressure is minimal. Peristalsis is almost wholly responsible for transport in this situation, whilst during the day the hydrostatic pressure of the height of the kidney above the bladder is enough to keep the urine flowing down the ureter with little help from the other two factors. In the wide ureter, with the body horizontal, peristalsis is ineffective and hydrostatic pressure absent. Transport here is wholly dependent on the pressure generated by the nephron.

It is of value now to take a closer look at peristalsis as although the overall effect of peristalsis in urine transport may be in doubt it seems clear from cystoscopic and radiographic evaluation that peristalsis plays an important role in propelling urine through the ureterovesical junction.

Figure 3 shows an analysis of local forces as a peristaltic wave propels a bolus of fluid down the ureter. Although the ureteric muscle is actually spirally orientated the contraction forces can be resolved into circular and longitudinal. There is a strong contraction of the circularly orientated muscle at the top of the bolus, with relaxation ahead of the bolus. The longitudinally orientated muscle contracts to pull the ureter up over the bolus—*an action which is effective only if the circular contractions have completely obliterated the lumen of the ureter.*

By peristalsis it is possible to conduct fluid down the normal ureter as localised areas of higher pressure—higher that is than the pressure within the renal pelvis. As the bolus reaches the ureterovesical junction the onward contractions of the circular muscle will drive the bolus through the orifice and at the same time the longitudinal muscle will help by pulling the last few millimetres of ureter up over the bolus (Fig. 4). By this coordinated action the orifice is pulled open to allow the bolus through.

It is probable that there is a minimum pressure, perhaps only a few centimetres of water, needed to open the orifice in the normal ureter. During a high diuresis (over 5 ml/minute/ureter) the whole upper tract becomes a continuous fluid column from pelvis to ureterovesical junction and the peristalsis at the lower end may finally be superseded by a continuous flow into the bladder. This is produced by a pressure within the whole upper tract which is sufficiently raised to constantly overcome the minimal resistance of the orifice.

The Mechanisms of Defective Transport in the Wide Ureter

In the wide ureter poor emptying may be attributable to one of, or a combination of, two factors. Firstly, the ureteric wall may be defective, perhaps congenitally, so that the walls are not apposed during attempts at peristalsis. Secondly, the ureterovesical junction may not open as it should.

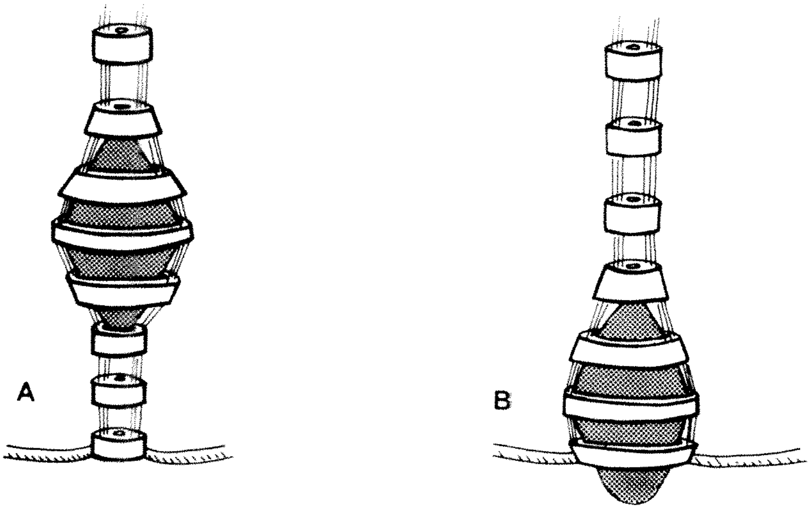


Fig. 4. Normal emptying of a bolus through the ureterovesical junction. A, Approaching the orifice. B, Passing through the orifice.

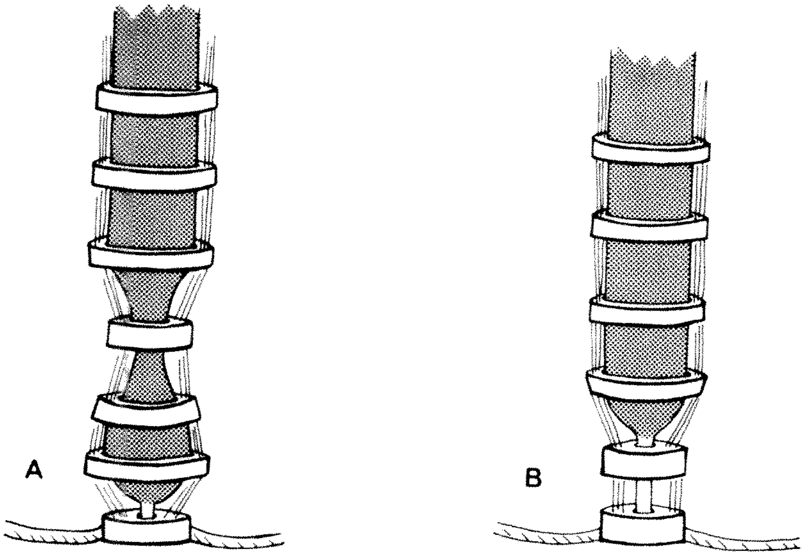


Fig. 5. Ineffective "peristalsis" at the lower end of a wide ureter. A, Downward moving contraction of circular muscle. The walls are not apposed and the "bolus" escapes upwards. B, Contraction of the circular muscle reaches the lower end and its unopposed action actively closes the orifice.

Although these may seem initially to be two separate factors it is not difficult to advance a theory to bind these two together as interdependent factors.

Bearing in mind the behaviour of the normal ureter (Fig. 4), the sequence of events in the wide lower ureter can be examined (Fig. 5). As a ureteric contraction passes down over the wide column of fluid it causes a to-and-fro movement with no overall onward progression of the fluid. As a bolus is not produced no localised area of pressure is generated to open the ureterovesical orifice, as described for the normal situation, but instead the fluid escapes upwards as the incompetent wave passes downwards. Also, because no bolus is formed the contraction of the longitudinal muscle is of no avail in contrast to its action in the normal situation.

The circular muscle, however, contracts in a downwards sequence until the orifice is reached. Here the ureter is of normal calibre and the walls are now apposed by the action of the circular fibres. Their contraction squeezes the lower ureter and prevents any fluid from passing through the orifice (Fig. 5, B). The potential bolus which the circular muscular action normally would have pushed through the orifice has escaped back up the ureter. This inadvertent or unopposed action of the circular muscle at the orifice acts to prevent the ureter emptying, and if as a result of this action the pressure in the ureter and renal pelvis is raised then the system is obstructed. In such functional obstruction, due to overactivity of an unopposed muscular action, there is no true mechanical narrowing and a probe can be passed easily through the orifice. An excess of circular muscle has been reported in the terminal portions of these wide ureters which supports this theory (Murnaghan, 1958*a*; Tanagho, Smith and Guthrie, 1970).

This theory can be advanced further to suggest that the situation could be self-perpetuating. A minor degree of obstruction caused by this unopposed action of the circular muscle leads to an increased pressure within the ureter, especially during a diuresis, and this will result in stronger action of the ureteric muscle to overcome the obstruction. The longitudinal muscle, as always in the wide ureter, is ineffective and the circular muscle contracts strongly but ineffectively until the wave reaches the orifice. Here it contracts more vigorously than ever and hence increases the resistance of the orifice, which in turn causes a higher pressure in the ureter. Furthermore, as the ureter dilates under the influence of this "functional" obstruction it comes to rely more and more for fluid transport on the pressure produced by the nephrons, which themselves have a limited capacity to produce pressure. Renal functional impairment then intervenes.

Thus peristalsis is probably an important factor in lower ureteric emptying. Its influence, however, is modified by a second factor—the resistance of the ureterovesical orifice.

In some wide ureters, at least, this resistance is no higher than normal and a combination of hydrostatic and nephron excretion pressure is sufficient to push the fluid through without peristaltic help. Such a ureter is not obstructed. In other wide ureters the resistance is raised. This may be because of inadvertent circular muscle contraction, with perhaps some resultant hypertrophy as discussed above, or because of an element of true narrowing.

The normal ureter with competent peristalsis can overcome *small* degrees of obstruction at the ureterovesical orifice by increasing the peristaltic pressure but without any increase in the pressure in the renal pelvis and thus without any adverse effect on the kidney. In the wide ureter, however, where emptying is dependent upon the pressure within the whole upper tract, a similar small increase in the resistance of the orifice necessitates a higher than normal pressure within the whole system and during a diuresis this pressure may be sufficiently high to damage the kidney.

A larger degree of obstruction converts a normal ureter to a wide one by changing effective peristalsis to ineffective ureteric activity. In the already wide ureter increased obstruction leads to further renal damage. Hence a small degree of obstruction does more harm in an already wide system than it does in a normal ureter.

The Pelviureteric Junction

Hydronephrosis as a result of the inability of the pelviureteric junction to conduct fluid correctly is a common phenomenon. The aetiology is still not clear. An increase in collagen tissue has been suggested by some (Murnaghan, 1958*b*; Notley, 1970) and abnormalities in the quality and arrangement of the musculature by others (Foote *et al.*, 1970), but these are inconsistent findings. The presence of vessels, adhesions, kinks, valves and the high insertion of the ureter on the renal pelvis have all been discussed (Murnaghan, 1958*b*; Johnston, 1969).

After all these have been excluded there are still some pelviureteric junctions which show no gross histological defects but are incapable of normal fluid conduction. It is to these that the following remarks refer.

A well executed pyeloplasty relieves the obstruction in the vast majority of cases and an analysis

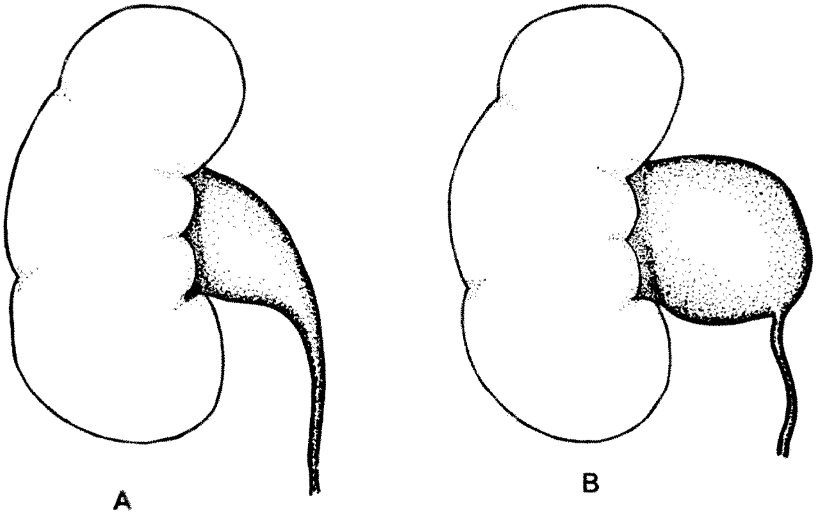


Fig. 6. Abnormal distension of the pelvis in the intermittent type of pelviureteric junction obstruction. A, At rest. B, With a fluid load.

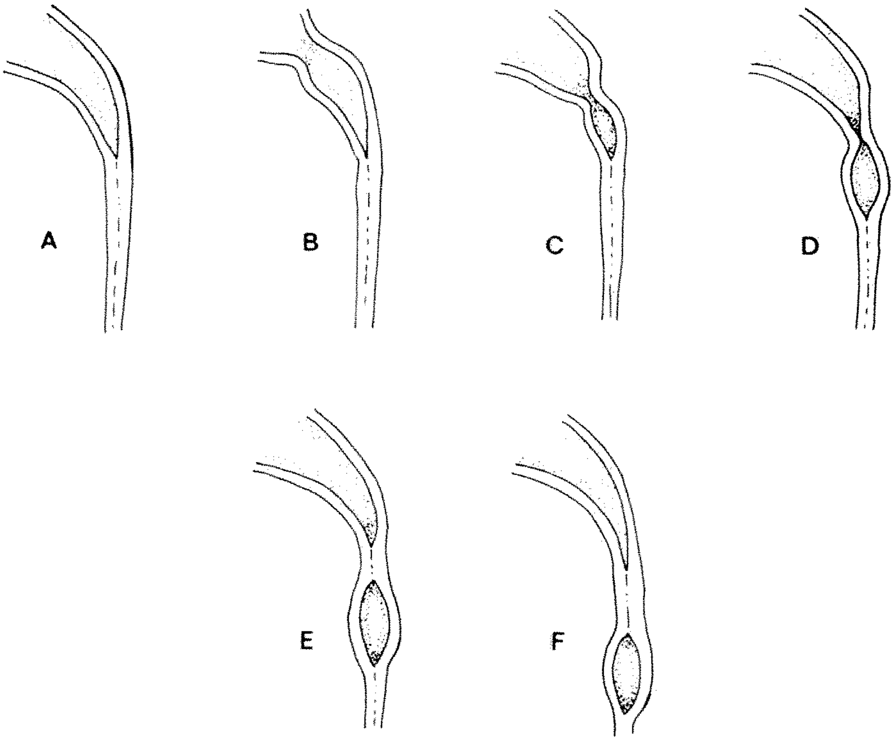


Fig. 7. Sequence of peristalsis at the normal pelviureteric junction.

of the effect of this operation gives a clue to the aetiology of the original obstruction. The operation results in a widening and tapering (funnelling) of the area between the renal pelvis and the upper ureter.

Normal Pelviureteric Emptying

The normal pelviureteric junction is inconspicuous and ill defined as there is a gradual tapering between the renal pelvis and the upper ureter (Fig. 6, A). It is this gradual tapering which makes it so effective as an emptying system. A contraction is initiated at a point somewhere within the pelvicalyceal system, often at the neck of a calyx. Whether this is due to a pacemaker or a local area of distension by the production of urine is immaterial to the present discussion. Some at least of these contractions reach the renal pelvis and pass down to the upper ureter (Fig. 7, A, B and C). In the lower part of the funnelled renal pelvis there is a point at which the downwards-moving contraction apposes the walls to form a bolus (Fig. 7, D).

Peristaltic activity, as discussed earlier, then carries the bolus on downwards (Fig. 7, E and F). Once the bolus is formed, the pressure within it can exceed the pressure within the renal pelvis (Kiil, 1957). The latter pressure can thus remain low and the kidney is protected.

Defective Pelviureteric Emptying

The lack of consistent or gross histological findings in the obstructed pelviureteric junction suggests that a search should be made elsewhere. One explanation is that the basic defect lies not at the junction but in the renal pelvis above. If the renal pelvis is abnormally distensible (Fig. 6, B), it rapidly loses its funnel shape to become more like a plug-hole in a bath. This is the more usual configuration in the obstructed junction. The larger the pelvis, the more likely will there be the problem of lower polar vessels and high ureteric insertion. A rapid diuresis or a slight compression from vessels can convert the renal pelvis from the configuration in Figure 6 A to that in Figure 6, B and this is seen in the intermittent type of hydronephrosis. Perfusion studies at the time of operation can show the true contribution to obstruction of the lower polar vessels (Whitaker, 1973).

The sequence of events during pelvic wall contractions in the abnormal renal pelvis is depicted in Figure 8. A wave of contraction passes along the rounded pelvic wall (Fig. 8, B, C, and D). At no point before the orifice do the walls meet to occlude the lumen and no bolus is formed. Because of this there is no appropriate muscle action to pull open the orifice (cf. section on lower end of wide ureter). The circular and longitudinal muscles have no bolus to grip on, and without a bolus their action is wasted, as it is only with a bolus formation that the orifice can be pulled open.

To make matters worse the contraction of the circular muscles continues down to the point at which the ureteric walls finally do meet at the orifice itself. Their action at this point is to close the hole firmly and actively prevent any fluid passing through.

The analogy with the lower ureter is obvious, but more than ever in the case of the pelviureteric junction is there a tendency for self-perpetuation. As the tension rises in the renal pelvis its walls contract harder and harder and the final squeeze of the circular muscle at the orifice is stronger and stronger. Thus the obstruction is due to an unopposed and inadvertent contraction of the circular muscle fibres at the pelviureteric junction. This contraction, however strong, can easily be overcome by passing a probe through the orifice at the time of a pyeloplasty. There is a gush of fluid as the probe is withdrawn, but this rapidly stops as the circular muscle again strongly contracts.

How does this situation resolve itself? After the diuresis, which has precipitated the overdistension of the renal pelvis and distortion of the pelviureteric junction, has abated, the pressure within the renal pelvis slowly drops. Initially, whilst the pressure is high the sheer tension in the pelvic walls pulls open the weakest point, which is the orifice leading to the ureter. Some fluid will passively drain out (Fig. 8, F). Pyelovenous and pyelolymphatic backflow may also help to

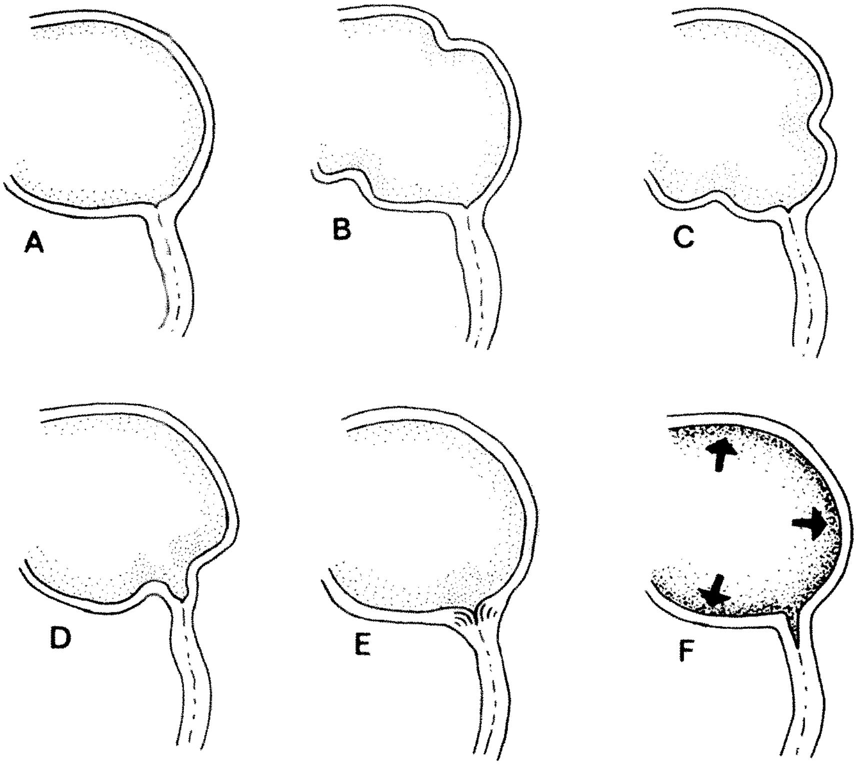


Fig. 8. Sequence of pelvic activity in the abnormal pelviureteric junction.

dissipate the pressure. Finally, at least in the intermittent type of pelviureteric obstruction, the shape of the pelvis returns to its original form (Fig. 6, A) and drainage will be satisfactory until the next attack.

Comment

In reference to the lower end of the wide ureter, Murnaghan (1958*a*) questioned whether the predominance of circular muscle was a primary abnormality or whether it was a selective hypertrophy secondary to some other intrinsic defect at the pelviureteric junction. The theory presented here is consistent with many of Murnaghan's findings, such as his perfusion studies and histological findings at the lower ureter. It is also consistent with the simple clinical and dynamic studies which can be made at the time of a pyeloplasty or reimplantation of a wide ureter.

Experiments will no doubt be designed to confirm or refute this theory, but in the meantime it provides a rational explanation for two puzzling clinical findings.

Summary

A simple but effective classification of the wide ureter is proposed. It separates ureters into two major groups of refluxing and non-refluxing, but emphasises that not all non-refluxing ureters are obstructed.

An analysis is made of normal and abnormal ureteric peristalsis and the part it plays in conducting a bolus through the pelviureteric and ureterovesical junctions. A theory is advanced to

explain the poor emptying of the wide ureter and the abnormal pelviureteric junction. It is based on the inability of the circular and longitudinal muscles to form a bolus and it explains how the unopposed and inadvertent contraction of the circular muscle grips the orifice in each situation to aggravate the poor emptying.

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Short Case Report

Bilateral Avulsion of the Upper Ureters

Avulsion of the upper ureter is a rare urinary tract injury. We report the case of a young girl who sustained bilateral avulsion which was recognised immediately, a satisfactory result being obtained with primary repair.

Case History

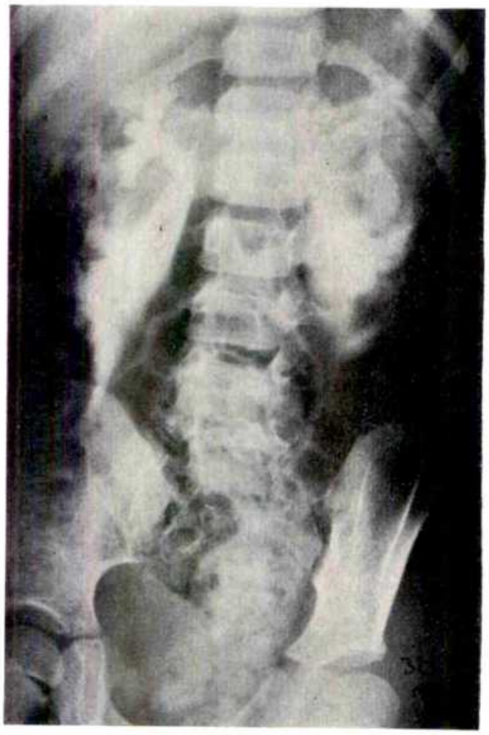
S. G., aged 3 years, fell from a car moving at 40 miles per hour but sustained only moderate external injuries. 4 hours later she developed painful flank distension. An intravenous pyelogram showed bilateral extravasation at the pelvi-ureteric junction (Fig.) and rupture at this level was diagnosed.

The ureters were explored trans-abdominally and the cleanly ruptured ends were found in collections of blood and urine. Oblique end-to-end anastomoses were performed over polyvinyl splints and the patient made an excellent recovery.

Comment

This injury is exceptionally rare and occurs predominantly in children under the age of 11 years (Boston and Smyth, 1975). Separation is almost always within one or two centimetres of the pelvi-ureteric junction. The diagnosis is often delayed, as in some reported cases for a month or more, particularly where severe multiple injuries co-exist. Intravenous pyelography is essential for diagnosis and reveals a characteristic appearance (Beckley and Waters, 1972).

Clinical features are unreliable in diagnosis, and haematuria, normally the commonest associated finding, was not seen in this case. A feature we consider was significant, however, was the lack of urine in the bladder on catheterisation or its subsequent production and this aspect has not previously received comment. No convincing explanation exists for the mechanism producing the injury, but the evidence from this case (tears in the posterior peritoneum) suggests a sudden traction on the ureter transmitted via the attached peritoneum from the rapidly moving abdominal viscera.



Acknowledgement

We thank Mr Neill Freeman for permission to report this case.

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Procidentia and Ureteric Obstruction

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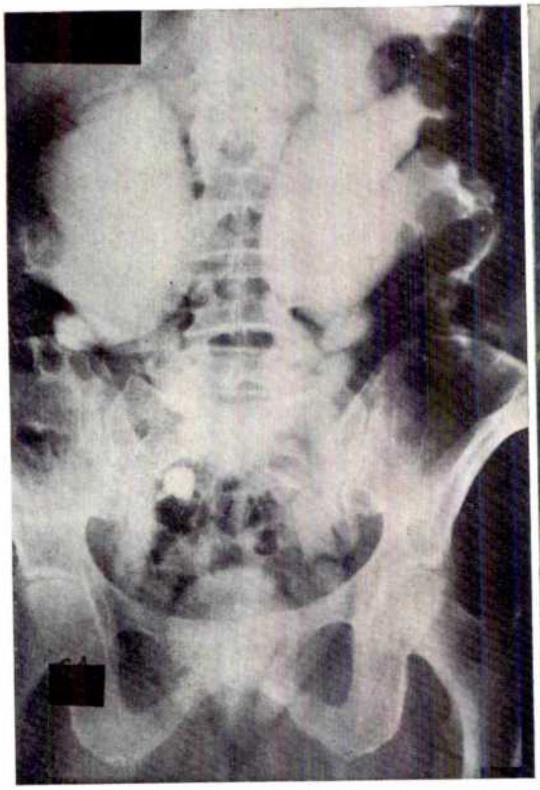
Although the incidence of procidentia is diminishing in most countries, it is far from rare. It is surprising how long the condition is tolerated before advice is sought. The complaint of the majority of patients is just that of the procidentia, and it is not until complications ensue that they present as emergencies.

The purpose of this communication is to highlight one such complication, renal failure, resulting from ureteric obstruction, which presented to the Department of Urology as an emergency in 3 patients. On reviewing asymptomatic cases of procidentia it was found that obstructive uropathy does occur in a small proportion of patients.

Case Presentation

Case 1

Mrs G. P., aged 71 years, presented as an emergency with urinary tract infection. Investigations revealed that she had a significant bacterial infection and a raised blood urea level (67 mg %). Previously she had been well. Physical



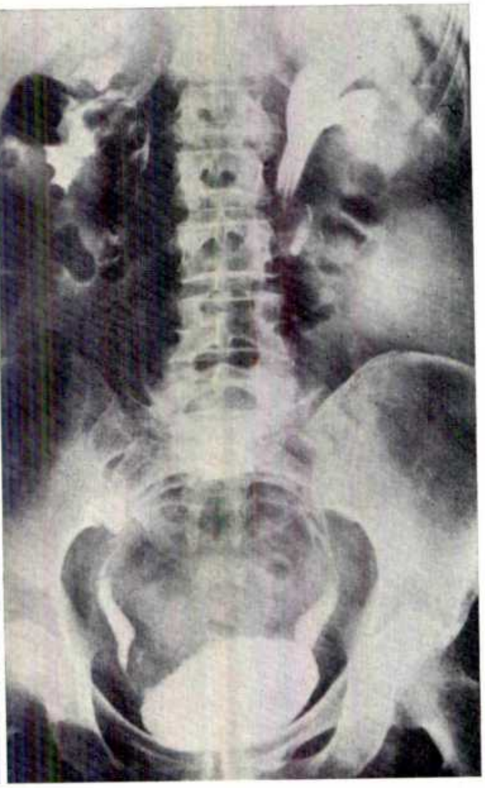


Fig. 1. Intravenous pyelogram performed on admission in the first case. The ureters can be seen passing out of the pelvis and are grossly dilated. The bladder is not dilated.

Fig. 2. A similar dose pyelogram performed 18 days later follow shelf pessary replacement of the procidentia.

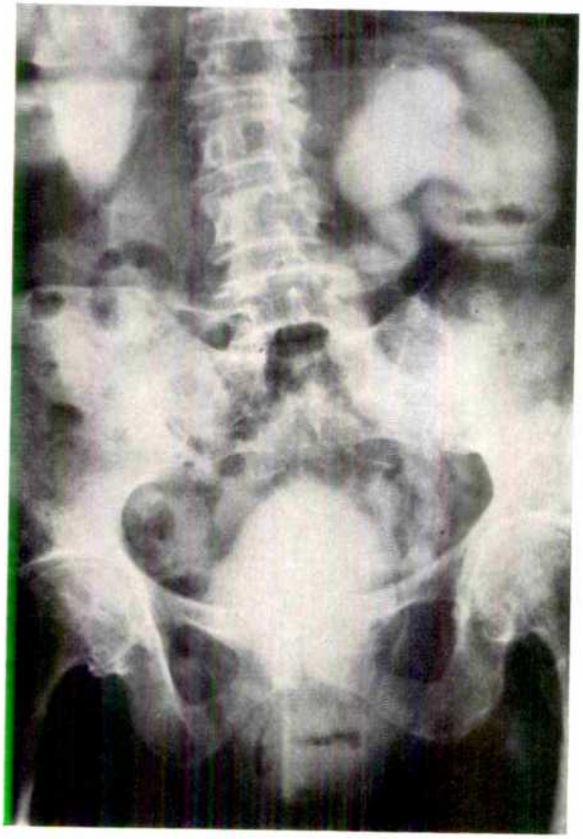


Fig. 3. Intravenous pyelographic appearances in the second case, demonstrating the gross upper tract dilatation and loss of renal substance.

examination was unrevealing apart from a long-standing untreated procidentia which had been present for 10 years. A high-dose intravenous pyelogram (IVP) (Fig. 1) showed enormous bilateral dilatation of the upper urinary tract; the bladder shadow, clearly seen passing out of the pelvis, although mis-shaped, was not dilated. The procidentia was replaced and kept in position with a shelf pessary whilst the urinary infection was treated with the appropriate antibiotic. A similar dose IVP performed 2 weeks later (Fig. 2) showed a dramatic improvement in the pyelographic appearances. Of interest are the mucosal foldings appearing in the previously dilated collecting system. A further pyelogram a year later showed a relatively normal urinary tract following vaginal hysterectomy.

Case 2

Mrs B. H., aged 74 years, presented severely dehydrated and in renal failure (blood urea 292 mg %). Physical examination showed a long-standing procidentia. A high-dose IVP showed considerable dilatation of the upper urinary tracts and loss of renal substance (Fig. 3). Also shown in this film is the rectal prolapse in the hernia, with gas shown outside the pelvis. Replacement of the procidentia and all attempts at resuscitation failed. Post-mortem examination was of interest; it showed that descent of the uterus out of the pelvis carried with it the base of the bladder along with the ureters, the latter impinging and apparently obstructing against the inferior pubic rami.

Case 3

Mrs C. A., aged 82 years, was admitted as an emergency with severe renal failure and dehydration (blood urea 320 mg %). A high-dose IVP showed a picture comparable to those already described. She was treated with shelf replacement of the procidentia and correction of her dehydration. By the time of her discharge 1 month later her blood urea level had fallen to 64 mg %. Six months later she underwent a vaginal hysterectomy with an uncomplicated recovery.

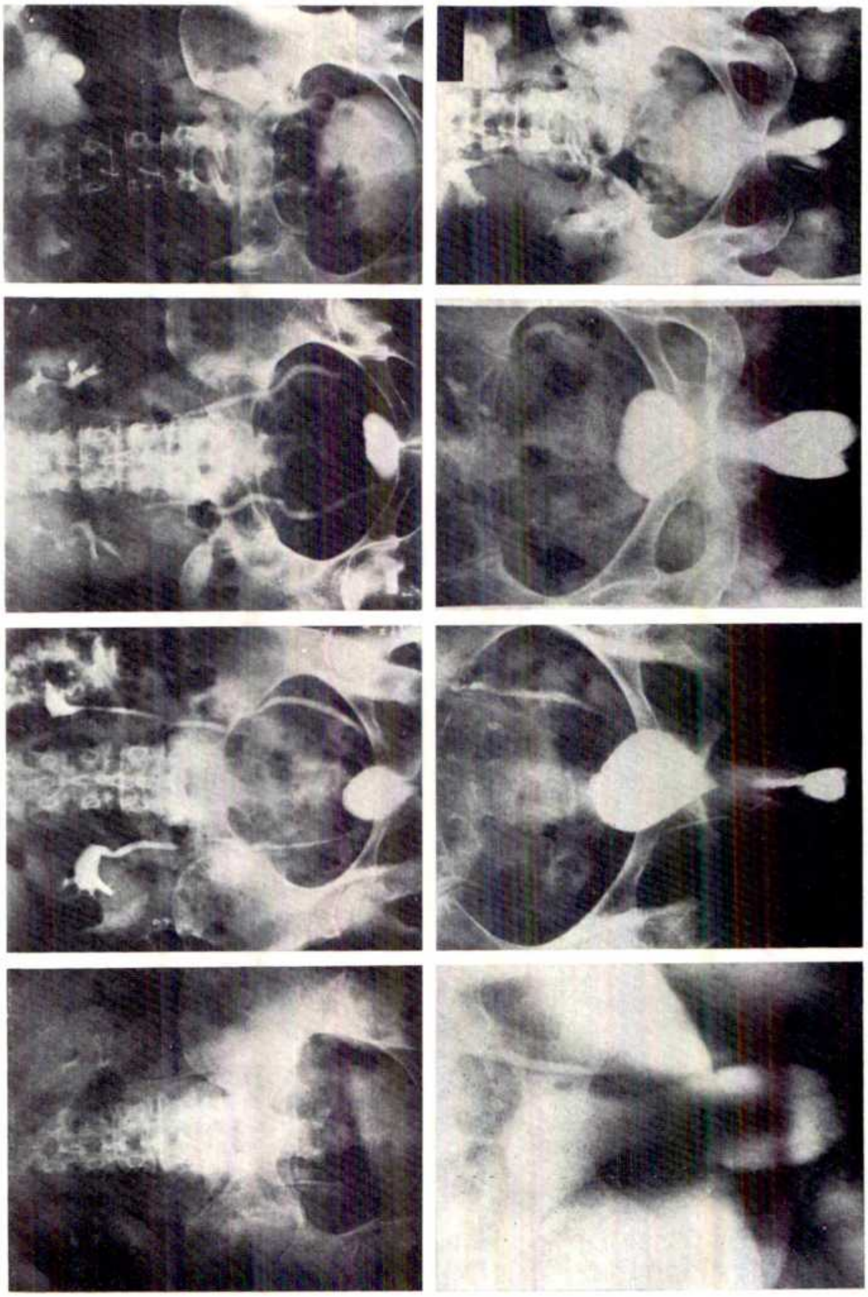


Fig. 4. The upper and lower urinary tracts in four asymptomatic cases of procidentia. Only in one is there any upper tract dilatation.

Discussion

Awareness of a condition is the mainstay of diagnosis. As we had not met this clinical entity before, we performed intravenous pyelograms on 4 asymptomatic patients with procidentia (Fig. 4). This shows the upper tracts and pelvic outlets in these cases. In only 1 is there any gross degree of upper tract dilatation.

The results of vaginal hysterectomy on the upper tract dilatation have been dramatic.

Froriep in 1824 first described renal failure resulting from uterine prolapse. Mueller-Heuback (1969) described 3 fatal cases and outlined theories to account for this condition. Halban and Tandler (1907) considered it to be due to ureteric compression against the lower border of the levator ani muscles, but this theory has not been supported by others. The commonest explanation is that of Brettauer and Ruben (1923), who postulated that the lower ends of the ureters were compressed by the uterine vessels in the inferior border of the broad ligaments. Of interest is that Millin (1949) found a high percentage of upper tract changes in uterine prolapse. We felt that the admission of 3 cases as emergencies within a few months of each other warranted further emphasis. In the one that came to post-mortem it appeared that the obstruction was against the inferior pubic rami. Whatever the cause, it would appear to be mechanical and is easily treated either by shelf or pessary replacement of the procidentia or by hysterectomy if the condition permits, preferably by the vaginal route. The risk of renal failure with procidentia appears to be small but would be avoided by early treatment of the condition. The intimate relationship of the ureters to the uterus in complete prolapse of this organ emphasises the need for pyelography in difficult cases.

Summary

3 cases of renal failure, due to procidentia, presenting as emergencies are described. The upper urinary tracts of 4 asymptomatic patients with procidentia were investigated; dilatation was found in 1 instance only.

We would like to thank Miss A. Bigby and Mr Harron Thomson for allowing us to study the latter cases in this presentation, also Dr D. A. L. Bowen who performed the autopsy on the second case: and Dr F. Pygott who stimulated us to collect and publish this series.

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The Value of Intestinal Valves in Urinary Diversion —an Experimental Study

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Although many methods of urinary diversion have been described in an attempt to overcome the problems of ascending pyelonephritis and electrolyte disturbances, these still remain largely unsolved. Bricker's urinary diversion (Bricker, 1950) by ileal conduit is generally accepted as the best method of minimising these problems, but the operation suffers from the disadvantages, both physical and psychological, of a cutaneous urinary fistula.

In 1957 Turnbull and Higgins described an ileal valve pouch formed by implanting the ureters into a 20-cm ileal loop whose distal end is everted to form a nipple which is then inserted into the sigmoid colon. This nipple forms a valve mechanism whose aim is to prevent colonic contents entering the ileal loop, thus avoiding the development of ascending pyelonephritis. In their series of 8 patients and in another of 12 (Houtappel, 1963) the short-term results were said to be good. However, this operation makes no attempt to deal with the problem of electrolyte disturbance, and Houtappel states that 50% of his patients required sodium citrate to preserve the alkali reserve.

An attempt to assess the effectiveness of this valve in experimental animals forms part of this study. We have also tested a similar valve, not previously described, between the colon and rectum whose purpose is to confine the urine to the rectum and prevent its reflux into the colon. In this way not only is the surface area of the large bowel mucosa with which urine is in contact reduced, but the urine is voided more frequently and completely. Theoretically, at least, both of these factors should reduce the reabsorption of electrolytes.

Methods and Material

The operation which is shown in diagrammatic form (Fig. 1) was carried out on 11- to 14-kg piglets. Anaesthesia was induced and maintained with halothane, nitrous oxide and oxygen without endotracheal intubation. An intravenous infusion was set up in the neck.

A midline abdominal incision was made and the rectum was mobilised. The ascending branch of the caudal mesenteric artery was divided, but it was found that division of the descending branch resulted in gangrene of the rectum, and so this vessel was subsequently preserved. The large bowel was then divided at the rectosigmoid junction and the free edge of the proximal bowel everted to form a 5- to 6-cm nipple which was then inserted into the rectum, and held in position with chromic catgut sutures (Fig. 2). A 20-cm loop of terminal ileum was isolated and a 5-cm nipple formed at its distal end. This was inserted into the anterior wall of the rectum below the colorectal valve. Both ureters were divided with minimal mobilisation just above the pelvic brim and the distal ends ligated. A longitudinal incision was made in the proximal cut end, so that the distal 1 cm of the ureter was spatulate, and this was then anastomosed to the ileal loop with continuous all layers 5/0 plain catgut sutures. No splintering catheter was used. The proximal end of the ileal loop was closed and fixed subcutaneously to facilitate urine sampling at a later date. The small bowel continuity was re-established and the abdomen closed. Antibiotics were not used.

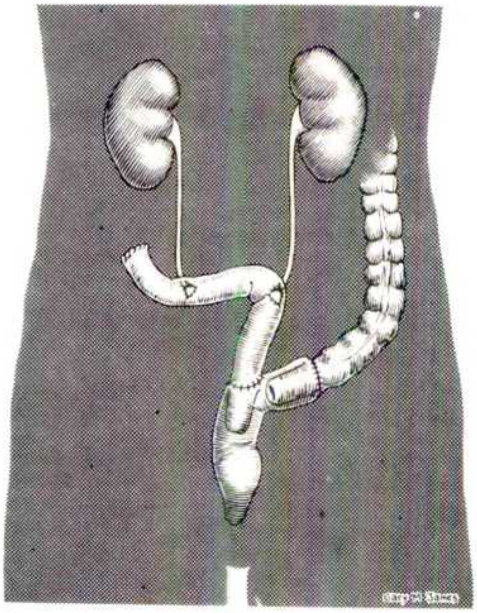

Fig. 1. Diagram of the completed operation.

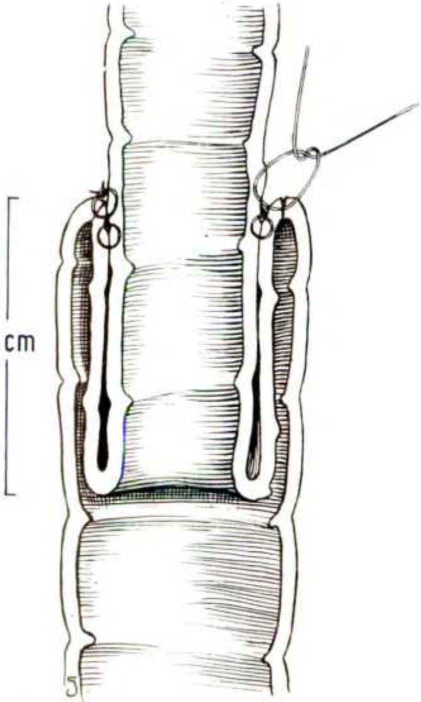

Fig. 2. Diagram of the intestinal valve.

One or more blood samples for blood urea and serum electrolyte estimations were taken at the time of operation, between the 8th and 12th week, between the 16th and 20th week and during the 26th week when the animals were killed.

Bacteriological studies were carried out on urine taken from the bladder at operation, from the ileal loop (under anaesthesia) between 8 and 12 weeks and between 16 and 20 weeks, and from the ileal loop and both renal pelves prior to sacrifice. The gross pathological and histological appearances of the kidneys were recorded at autopsy.

Intravenous pyelography and barium enema studies were performed simultaneously (under anaesthesia) between 3 and 6 weeks and repeated in the 4th postoperative month. The residual urine in the rectum was measured at this time under anaesthesia after the rectum had been voluntarily evacuated.

21 pigs were operated on. Of these, the full operation was performed on 14, in 6 the colorectal valve was excluded and in 1 the colorectal valve only was constructed. 9 pigs died within the first postoperative week and were therefore not available for further study. Of these early deaths, 5 were due to stenosis at the uretero-ileal anastomosis or to ureteric ischaemia. This problem was encountered early in the series and was avoided thereafter by adopting the technique of anastomosis described in the text. The causes of death in the remaining 4 animals were arterial infarction of the rectum, venous infarction of the rectum, air embolus and aspiration pneumonia.

Of the remaining 12 pigs, 7 were only partially studied. 2 died of small bowel volvulus in the 6th and 12th week, and 5 died of pyelonephritis between the 1st and 5th month. Of these, 3 had debris partly obstructing the lower ureter but 2 had no evidence of obstruction. In all 5 the ileorectal valve was competent to barium.

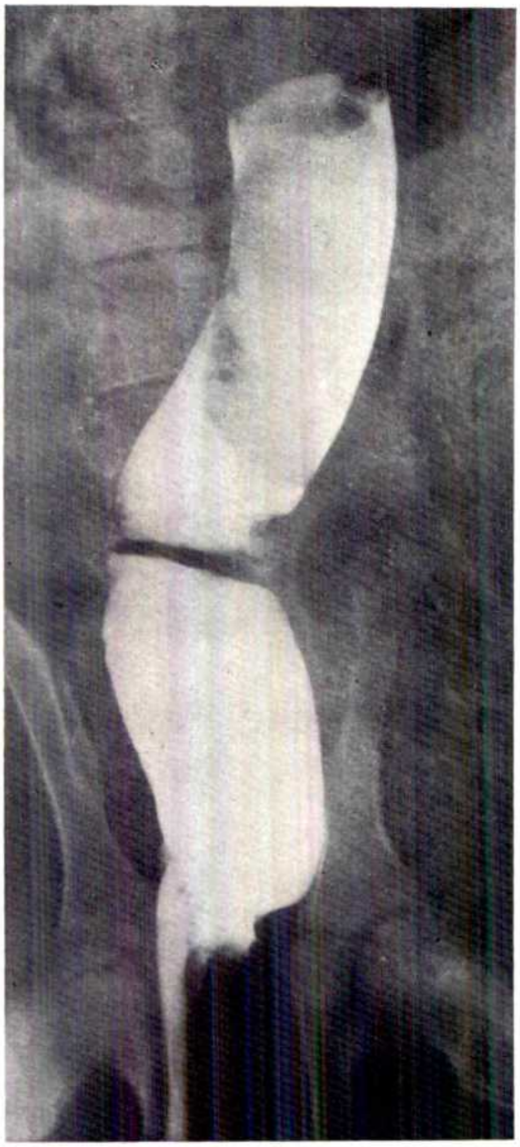

Fig. 3. Barium enema appearances of a competent colorectal valve.

Results

Valve Competence

Ileorectal Valve

Of the 7 ileorectal valves fully investigated, 6 were competent to a barium suspension run into the rectum from a height of 50 cm. The 7th was observed to invert and become incompetent during the radiological investigation and thereafter remained incompetent. However, gas was observed in the urinary tract in 4 animals, although this did not appear until the 4th month in 1 case. Bacteriological studies indicated that this gas was unlikely to be due to gas-producing organisms within the urinary tract, and it is probable that it represented a valve intermittently incompetent to gas.

Colorectal Valve

Of the 7 colorectal valves fully investigated, 5 remained competent to barium, only the first 2, done before the technique of construction had been perfected, being incompetent.

There was no evidence of obstruction at either valve. The typical radiological appearances of a colorectal valve is shown (Fig. 3) and a description of the radiological methods of investigation and the appearances of these valves form the basis of a separate paper (Ratcliffe, Knox and Jago).

Accurate measurement of residual volumes of rectal fluid in the animals without competent colorectal valves proved impossible due to the admixture of urine and faeces. However, the residual volume in the pigs with competent colorectal valves was more easily measured and was less than 15 ml in each case.

Electrolytes

The electrolyte estimations were divided into 3 groups. Group I comprised those obtained from the animals preoperatively and were used as controls, group II were those obtained from animals with competent colorectal valves, and group III were those from pigs with absent or incompetent colorectal valves. The results (Table I) were analysed by an analysis of variance. No difference was found between the groups when potassium and chloride levels were considered. The urea was significantly raised from normal in both groups II and III, but did not differ significantly between these 2 groups. The bicarbonate levels were lower in the pigs without competent colorectal valves when compared with the normal animals and those with competent valves. These differences are highly significant (Table II) and indicate that the colorectal valve protected the animals against the development of acidosis.

Table I

Electrolytes	Group I normal	Group II competent valves	Group III no valves
K$^+$ (mEq/litre)	4·2 ± 0·08 (14)	4·1 ± 0·20 (7)	4·3 ± 0·23 (5)
Cl$^-$ (MEq/litre)	98·6 ± 0·80 (15)	95·9 ± 1·77 (10)	98·1 ± 1·97 (9)
Urea (mg/100 ml)	24·5 ± 1·25 (15)	60·0 ± 7·43 (10)	72·3 ± 16·79 (9)
HCO$_3^-$ (mEq/litre)	25·8 ± 0·78 (15)	24·6 ± 1·43 (10)	19·3 ± 0·94 (9)

Means of electrolyte estimations carried out ± standard error.

Infection

22 kidneys in 11 pigs were available for study. All conduits contained infected urine, although in 2 cases the urine contained less than 4 white cells per high power field at all times. Infection, however, tended to become more severe with the passage of time. Renal infection was considered to be mild if the urine contained less than 4 white cells per high power field, the kidneys were macroscopically normal and the microscopic changes of pyelonephritis were minimal. Those with moderate or gross features of pyelonephritis were grouped together. The findings are shown in Table III. Severity of infection did not correlate with presence of gas bubbles in urinary tract seen on intravenous pyelography.

Table II

	F	P
Normals/ Competent valves (Group I) (Group II)	0·70	>0·05
Normals/ No valves (Group I) (Group III)	27·8	<0·001
Competent valves/No valves (Group II) (Group III)	9·34	<0·001

Comparison of bicarbonate estimations for the groups studied.

Table III

Degree of Pyelonephritis following Operation
(All pigs survived at least 1 month)

Severity of infection	No. of kidneys	No. of kidneys examined at 6 months
Mild	9	3
Moderate or severe No obstruction	9*	5*
Moderate or severe Partial ureteric obstruction with debris	4	—

* Includes pig with incompetent ileorectal valve.

Discussion

Although in 2 series (Turnbull and Higgins, 1957; Houtappel, 1963) good results are reported following the operation of uretero-ileosigmoidostomy, the follow-up periods were short and no detailed bacteriological studies were done on their patients. Moreover, experimental work using dogs indicates that the uretero-ileosigmoidostomy operation had no advantage over uretero-sigmoidostomy (Moors *et al.*, 1973). In this study a polyethylene splinting catheter was used in the uretero-ileal anastomosis and it is not made clear whether this was removed or not. If it were not, the presence of a foreign body in the urinary collecting system would make the results difficult to interpret. In our series there was some degree of infection in all kidneys.

The ileorectal valve was demonstrably incompetent in 1 case, but even when the valves were grossly competent the presence of gas bubbles in the urinary tract indicates that, in some cases at least, competence is incomplete. Reliance has been placed on the peristaltic action of the ileal loop to prevent ascending infection in the operation of non-valved uretero-ileosigmoidostomy (Pinck, 1969), but in at least half of these cases there was evidence of gross reflux. We have shown that the ileorectal valve cannot be relied upon to prevent ascending infection. The results of uretero-ileosigmoidostomy have yet to be compared with Bricker's ileal conduit in which an infection rate of from between 56% (Kafetsioulis and Swinney, 1968) to 70% (Small, Boyarsky and Glenn, 1968) has been recorded.

The electrolyte abnormalities associated with urinary diversion into the intestinal tract have been shown to occur even in the presence of normal renal function (Stamey, 1956). The most important factors affecting electrolyte absorption are the surface area of intestinal mucosa exposed to the urine and the time during which the urine is in contact with the mucosa (Hopewell, 1959). For many years it has been recognised that most of the urine is stored above the rectum as far back as the caecum following uretero-sigmoidostomy and that evacuation of this urine is incomplete. Electrolyte disturbances should therefore be reduced if urine is limited to the rectum, and is evacuated completely and frequently. This study has shown that the fashioning of a competent colorectal valve is possible in the experimental animal and that it achieves this objective. Furthermore, although there was a statistically significant reduction in the serum bicarbonate levels in animals without competent colorectal valves when compared with normal, estimations of serum bicarbonate levels in those animals with competent colorectal valves did not statistically differ from normal. It can be concluded, therefore, that the colorectal valve, in experimental animals at least, is effective in preventing the development of acidosis. It has been noted that electrolyte abnormalities are encountered less frequently following uretero-sigmoidostomy in children than in adults (Mitchell, 1974). Our experiments have been carried out on piglets and the electrolyte changes might have been more severe had the operation been done on adult pigs. However, there is nothing in our results to suggest that the protective effect of the colorectal valve would have been less marked in this case.

The high mortality in our series is in part due to technical problems encountered early in our experiments and subsequently solved, and in part due to general complications not associated with this operation in particular. 5 pigs died of pyelonephritis after an otherwise satisfactory operation, but it is interesting to note that there were no life-threatening complications attributable to the intestinal valves themselves. Other workers have encountered a very high mortality in dogs following implantation of both ureters into the ileum in the operation of uretero-ileosigmoidostomy (Abbott *et al.*, 1961). Moors and his colleagues were confronted with the same problem, and overcame it by implanting 1 ureter only in their experiments. By comparison, our results are relatively good and may reflect the greater suitability of piglets for this work. The mortality of this operation in clinical practice has yet to be established, but the experience of Turnbull and Higgins and of Houtappel leads us to believe that it would be acceptable.

Summary

It has been shown in experimental animals that an ileorectal valve incorporated into the operation of uretero-ileosigmoidostomy cannot be relied upon to prevent ascending urinary tract infection.

However, a colorectal valve, not previously described, has been effective in preventing the development of a metabolic acidosis in piglets in whom this method of urinary diversion has been carried out.

We should like to thank the South Western Regional Hospital Board who supported this work with a grant and Ethicon Limited for supporting preliminary work by one of us (R. H. J.).

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Short Case Report

Cystitis Glandularis causing Bilateral Ureteric Obstruction and Hydronephrosis

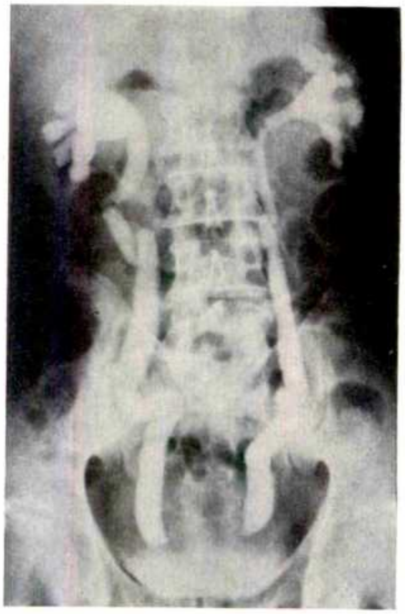
Cystitis glandularis is an unusual condition in which proliferative glandular elements occur in the mucosa and submucosa of the bladder. A rare complication is that of bilateral ureteric obstruction leading to hydronephrosis and kidney damage. 2 such cases have been reported in the literature so far (Roll, 1960; Blum, 1966) and herein is reported the third case.

Case Report

A 48-year-old white male was admitted with colicky pain in both costovertebral angles of 2 days' duration. 2 days prior to the onset of pain the patient had dysuria and frequency. Physical examination revealed tenderness in both flanks. Urinalysis showed 8-10 RBC's and WBC's, but there was no growth in culture. An IVP revealed bilateral hydroureters and hydronephrosis (Fig.). Voiding cystogram was normal. Pan-endoscopy revealed a normal urethra, but the interior of the bladder showed a brownish granular appearance of the trigone and the internal urethral orifice. The ureteric orifices could not be made out. The rest of the bladder was clear and the capacity was normal. Multiple biopsies from the area of the trigone were performed. The histology of the specimen showed solid buds of epithelium (Brunn's nests) and extensive cyst formation with mucoid stroma in the submucosa. The patient's symptoms and the IVP did not show any improvement even after 6 weeks of antibiotic therapy and it was decided to explore the bladder and re-implant the ureters. He did well postoperatively and an IVP 1 year later showed a remarkable reduction in the hydronephrosis and hydroureters. The patient continues to do well and is being reviewed every 6 months.

Comment

The aetiology of this condition is not clear though chronic urinary tract irritation due to various combinations of infection, obstruction and stone formation may be factors in its causation.



In treating cases of bilateral ureteric obstruction caused by cystitis glandularis certain points have to be emphasised because of the presence of dense periureteric induration in these cases: (1) bilateral meatotomies however wide are inadequate; (2) the ureters should be sectioned well proximal to the intramural portions and re-implanted in a healthy area; (3) if the whole bladder is involved then a cystectomy and urinary diversion should be done.

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An Improved Surgical Technique for Intra-vesical Resection of Bladder Diverticula

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Even though vesical diverticula may be somewhat adherent to the peri-vesical adventitia, their entire structure is frequently represented by the single layer of bladder mucosa that has herniated outside the bladder. Except for the orifice itself, this is the only tissue that need be removed surgically.

While the extra-vesical approach may be satisfactory for those diverticula arising from the superior aspect of the bladder (Goldman, 1971), it may be hazardous for the more common para-ureteral or trigonal diverticula arising from the low posterior aspect of the bladder. An extra-vesical approach in this situation, particularly if there are bilateral diverticula, runs the risk of injury to the innervation of the bladder. The intra-vesical technique most commonly recommended consists of grasping the mucosa of the diverticulum through its orifice, inverting it into the bladder, excising the mucosa and closing the muscular defect. While this technique has worked well in many patients, damage to adjacent vital structures such as the ureter or the vas deferens may occur when the diverticulum is either quite large or in a para-ureteral location. An improved surgical technique that will prevent such occurrences is described below.

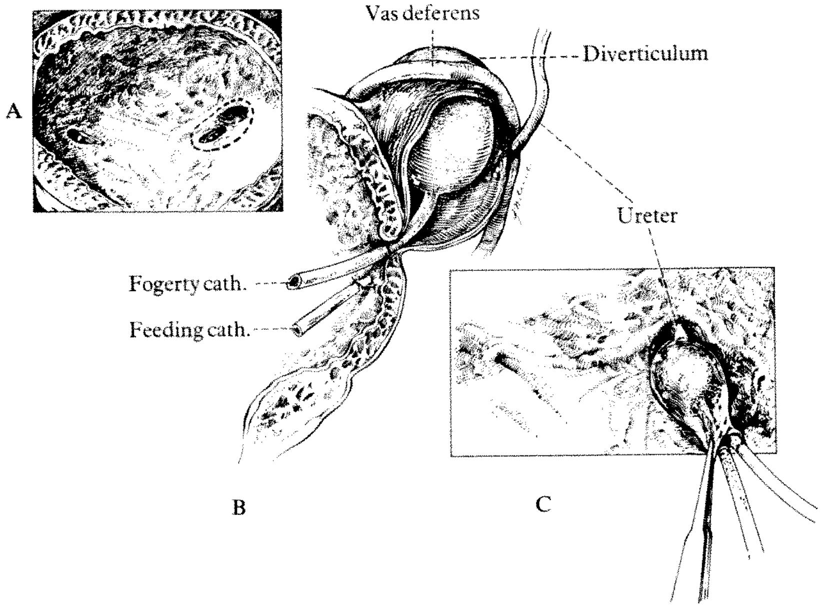

Fig. 1. A, The opened bladder showing the two ureteral orifices and the orifice of the diverticulum above and lateral to the left ureteric orifice. B, A small Fogarty catheter has been secured in the orifice of the diverticulum and a small feeding tube is in place in the ureteric orifice. C, A circumscribing incision has been made about both orifices and dissection carried out on the surface of the herniated mucosa that comprises the diverticulum.

Technique

The bladder is approached and opened. The ureteral orifices and the orifice of the diverticulum are identified (Fig. 1, A). In the absence of reflux or obstruction and if the orifice of the diverticulum is over 1 cm from either ureteric orifice, a purse-string suture is placed in its margin. Either a small Foley catheter or a Fogarty catheter is placed within the diverticulum and secured in place with the previously placed purse-string suture. The catheter balloon is inflated by an amount appropriate to the size of the diverticulum. A circumcising incision is made around the orifice of the diverticulum similar to the one made at the start of a Politano-Leadbetter type of reimplantation. Dissection is carried through the bladder wall and then continued on the outer surface of the mucosa of the diverticulum. The inflated balloon within the diverticulum helps to delineate this plane of dissection. While there may be an occasional muscle fibre on the outer surface of the diverticulum, the plane of dissection is easily maintained between the single layer of mucosa and the peri-vesical adventitia. As one continues this dissection more and more of the diverticulum is drawn into the bladder making the dissection easier (Fig. 1, C). Changing the degree of inflation of the balloon within the diverticulum will facilitate completion of the dissection. Eventually the entire intact diverticulum will be free within the bladder and the muscular defect through which the herniation occurred will be clearly seen. This and the overlying mucosa can be closed with interrupted sutures. If upon opening the bladder the orifice of the diverticulum is in close proximity to one of the ureteric orifices, or in the presence of vesicoureteral reflux or obstruction, a catheter or plastic feeding tube is sutured into the involved ureter in addition to the catheter within the diverticulum (Fig. 1, B). In this situation the ureter is so intimately associated with the diverticulum that an attempt to excise the diverticulum separately may lead to injury to the ureter. The vas deferens runs on the medial aspect of the diverticulum and can easily be seen and preserved as the dissection continues. After the diverticulum and adjacent distal ureter are excised the muscular defect is closed and a standard reimplantation carried out.

Summary

A technique for the resection of bladder diverticula which lessens the chance of injury to the ureter, vas deferens or the innervation of the bladder is described.

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Malignant Phaeochromocytoma of the Urinary Bladder—Report of Two Cases

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Malignant phaeochromocytoma of the urinary bladder is an extremely rare occurrence, only 4 patients so far having been reported. Two new cases have been observed here at the Pahlavi University. Pelvic angiography was performed for the first time in this condition.

Case Reports

Case 1. G. A., a 44-year-old white male was admitted to Nemazee Hospital, Pahlavi University on 2nd October with a history of painless haematuria of 2 months duration. Physical examination revealed blood pressure of 180/100. IVP demonstrated a large filling defect in the bladder (Fig. 1). Pelvic angiography indicated innumerable pathological vessels and tumour stain (Fig. 2, A and B). Cystoscopy revealed a nodular tumour in the dome of the bladder 2 × 2 cm in diameter. At operation a large vesical tumour was found. Interestingly enough, the major part of this mass extended outside the bladder wall. Partial cystectomy and resection of two large lymph nodes along the external iliac artery were performed. Histological examination of the bladder tumour and the resected lymph nodes disclosed phaeochromocytoma. Postoperatively, the BP returned to 120/70 and remained at that level for 3 months. He was lost to follow-up and a year later died suddenly.

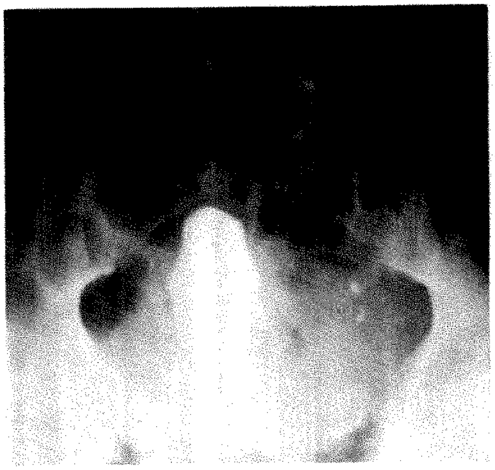

Fig. 1. IVP. Case 1: large filling defect in the bladder.

Case 2. S. M., a 24-year-old female known to be hypertensive for 3 years was admitted to Pahlavi University, Saadi Hospital on 7th March 1973. She complained of headache, dizziness, palpitation, shortness of breath, profuse sweating, hot flushing, nausea and vomiting. These symptoms occurred primarily during the last month of each of the last 3 pregnancies during the last 3 years. Following her last delivery (40 days prior to admission), the clinical symptoms became persistent and were particularly aggravated at the time of urination. She had 2 episodes of fainting while urinating. Her blood pressure ranged between 150/110 to 250/130. Pelvic examination disclosed the presence of an orange-size tumour. Bimanual palpation of this mass caused sudden increase of blood pressure and rapid pulse rate. Urinalysis was normal and 24 hours excretion of urinary vanillyl mandelic acid was 18·6 mg. IVP presented medial deviation of the left ureter suggestive of an extrinsic mass laterally (Fig. 3). Cystoscopy demonstrated intact bladder mucosa with no gross pathology inside.

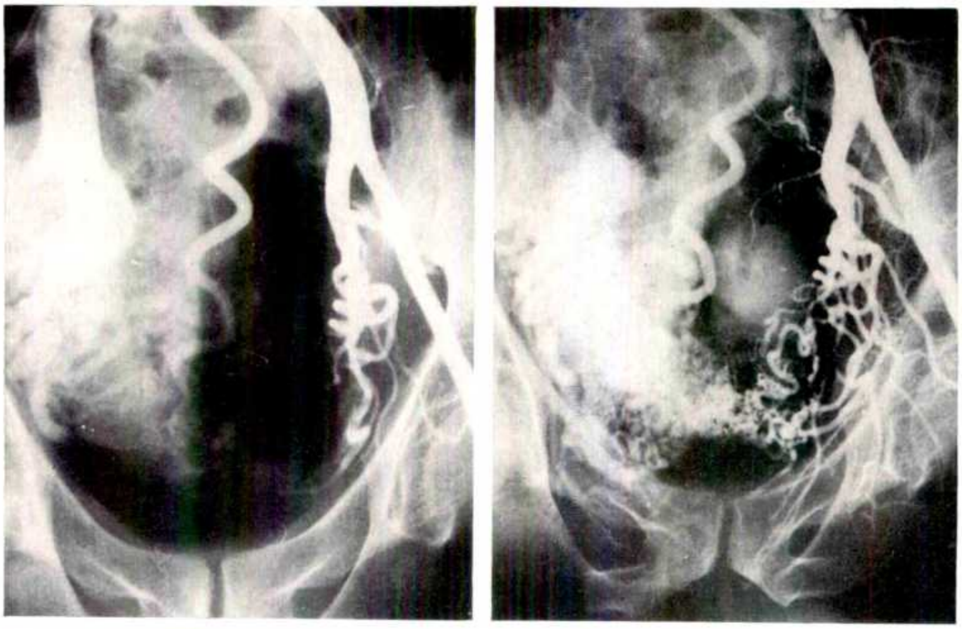

Fig. 2. Pelvic angiography. Case 1: demonstrating pathologic tumour vessels (A) and tumour stain (B).

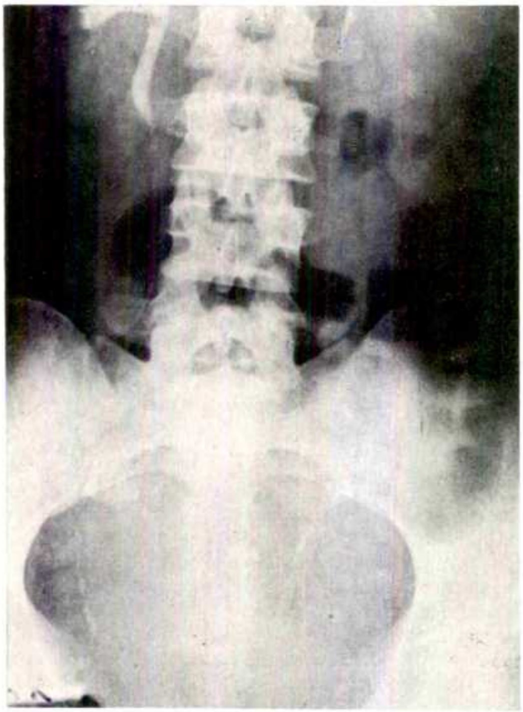

Fig. 3. IVP. Case 2: medial deviation of the left ureter suggestive of an extrinsic mass laterally.

Both adrenal glands appeared normal on exploration. The palpated pelvic tumour arose from the external surface of the bladder without invasion of the vesical mucosa. Partial cystectomy along with resection of 2 enlarged adjacent lymph nodes were performed. Histological examination of the resected mass and the lymph nodes disclosed phaeochromocytoma. Her clinical symptoms completely subsided after the operation and her BP returned to 110/70. She is now on her 1-year follow-up and has remained normotensive and asymptomatic.

Discussion

Since Zimmerman, Biron and MacMahon (1953) presented the first case of phaeochromocytoma of the urinary bladder, 38 cases have been reported in the literature, (Cabanas, Faulconer and Fekete, 1973). Four of these 38 cases have been malignant. The first malignant case, (Pugh, Gresham and Mullaney, 1969) was a 36-year-old female who died shortly after cystoscopy and at autopsy she was found to have phaeochromocytoma of the bladder with metastasis to the regional lymph nodes and the liver.

The second case (Higgins and Tresidder, 1966) was a 14-year-old boy with haematuria and sustained hypertension. Partial cystectomy and resection of metastatic regional lymph nodes were performed. The patient was known to be normotensive and doing well at 9 months after operation.

The third malignant case (Moloney, Cowdell and Lewis, 1966) was a 26-year-old male with metastasis to lymph nodes, lungs and bones. Partial cystectomy was done; but he died 4 years after the treatment.

The fourth patient (Scott and Eversole, 1960) was a 14-year-old white boy who had sustained mild hypertension. Total cystectomy, prostatectomy, seminal vesiculectomy and urinary diversion were performed. A regional lymph node was invaded with the same type of tumour. The patient was known to be alive and well 14 months after surgery.

Our 2 cases bring the total number of malignant cases of phaeochromocytoma of the bladder to 6. The only evidence of malignancy in this disease is the presence of metastasis because histological changes and tissue infiltration also may be seen in tumours with quite benign behaviour (Doctor, Phadke and Sirsat, 1972). Vesical phaeochromocytoma originates from the paraganglia related to autonomic nerves which are mainly located in the muscular layer of the bladder wall, (Bourne and Beltaos, 1967). The mucosal layer may look intact in this type of bladder tumour. Cystoscopy may or may not reveal the presence of tumour. In our first case cystoscopy revealed the mass while in the second case cystoscopy failed to show any pathology. Tumours of phaeochromocytoma arise from chromaffin tissue and in 10% of the cases are multifocal (Higgins and Tresidder, 1966). Multifocal tumours should not be mistaken for metastasis. The tumour is defined as multifocal if, besides the original tumour, another mass is located at sites where chromaffin tissue naturally is present. The metastasis of phaeochromocytoma invades tissues that normally do not have chromaffin elements. Partial cystectomy is the recommended type of treatment. Since the tumour is situated between the muscular fibres of bladder wall and does not necessarily invade the mucosal layers, transurethral resection does not seem to be the satisfactory treatment. Radiation has been used in the treatment of malignant phaeochromocytoma (Higgins and Tresidder, 1966). It is too early to judge the effectiveness of this therapy.

Summary

2 new patients with malignant phaeochromocytoma of the urinary bladder were presented.

4 other cases with the same disease reported in literature were reviewed and discussed.

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False Cytodiagnosis of Bladder Malignancy due to Previous Radiotherapy

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It is known that irradiation of the cervix uteri produces changes in the cervical epithelium which subsequently exfoliates bizarre cells whose appearances resemble malignant ones (Wachtel, 1964; Koss, 1968, pp. 277-281). Post-radiotherapy cytological appearances therefore become difficult, if not impossible, to interpret when examinations are made to determine whether a growth has been eradicated or has recurred. A comparable situation exists in the case of malignant bladders which have been irradiated (Koss, 1968, p. 413) and experience of this has been reported in a previous paper (Cowen, 1971). Seybolt (1960), Goodman and Balfour (1964) and Esposti, Moberger and Zajicek (1970) mention radiation changes in bladder epithelial cells but do not specify the features that distinguish non-irradiated malignant cells from non-malignant ones altered by irradiation. More recently, Loveless (1973) made a particular study of the effects of radiation on benign and malignant bladder epithelia and gave cytological criteria for distinguishing malignant from irradiated benign cells.

The present study was undertaken to assess this problem which we frequently encounter in undertaking a urological cytodiagnosis service for the General Infirmary at Leeds.

Procedures

The details of our cytodiagnosis service, including preparation of specimens and cytological criteria of malignancy, have already been described (Cowen, 1971). All urine specimens which were received during the 6 survey years, 1st November 1967 to 31st October 1973, and which had been sent with the information that the patient had received previous radiotherapy, were investigated. The specimens which had been reported to contain malignant cells (positives and suspects) but whose donors had no clinical or histological evidence of new growth in the urinary tract at least 2 years later, were classified as false positives or false suspect results. All these microscopic preparations were reviewed to see if the appearances of the cells which led to the positive or suspect report had features which would distinguish them from malignant cells exfoliated from non-irradiated bladder carcinomata. The histology of the bladder biopsies following these cytology examinations was also reviewed.

Results

A total of 3,855 urine specimens was received during the 6 survey years. Of these, 692 were reported as showing cells which were either malignant or suspect of being malignant. The request cards accompanying 52 of these informed us that the patients had been previously treated by radiotherapy. A follow-up survey of these patients was made and in the case of 9 out of these 52 specimens, no evidence of new growth in the donor's urinary tract was present at 2 years or longer after the cytological examination. These 9 specimens, which came from 7 patients, were classed as false positives or false suspects and relevant details are shown in the Table.

The slides of these specimens were reviewed and the appearances of the abnormal cells were reassessed. Using our criteria of malignancy (Cowen, 1971 and listed in the present Discussion),

Table

Details of the 9 False Positives and False Suspect Specimens

Patient No.	Specimen No.	Reported as	Time (months) between last radiotherapy and cytological examination	Follow-up time (months)*
1	1	Positive	39	32
1	2	Suspect	36	29
2	3	Positive	6	29
2	4	Positive	12	23
3	5	Suspect	5	77
4	6	Positive	9	24
5	7	Suspect	52	41
6	8	Suspect	2	32
7	9	Suspect	6	24

* The time between the cytological examination and the clinical or histological examination when a new growth was excluded.

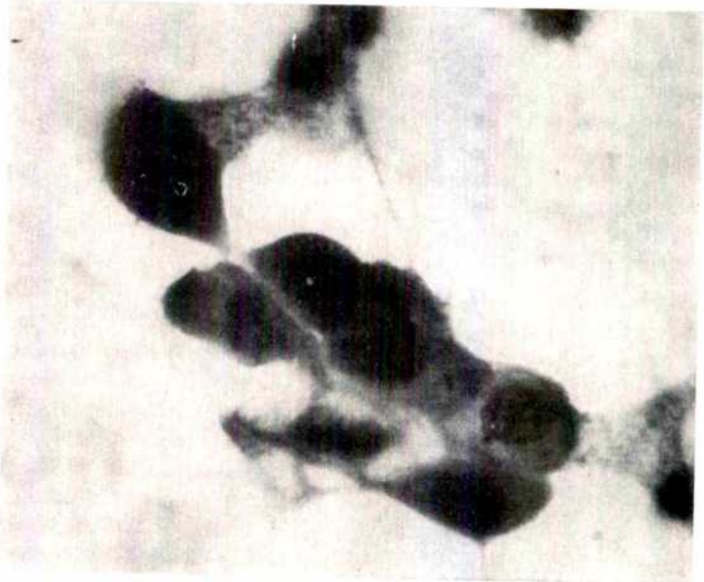

Fig. 1. Specimen 2. A clump of cells showing pleomorphism, anisocytosis and hyperchromatic nuclei. One cell is degenerate with vacuolated cytoplasm. (All preparations are stained haematoxylin and eosin. Figures 1-10 are × 980.)

it was concluded that these cells had features which justified classifying them as malignant or being suspect. No stigmata were found which might indicate specific radiation changes. Representative examples of these cells are shown in Figures 1-10.

Bladder biopsies were taken from patients 3, 4, 6 and 7 (two biopsies from 3 and one from each of the others) at various times after the cytological examinations of the urines. No new growth was seen in any. No epithelium was present in either biopsy from patient 3, due to post-irradiation ulceration. The biopsies from patients 4, 6 and 7 were taken at 7, 9 and 14 months respectively after the urines had been examined, and besides the non-specific inflammatory changes due to the irradiation, the epithelia showed distinct dysplastic changes with nuclear hyperchromatism, and variation in nuclear and cell size, mainly enlargement (Fig. 11).

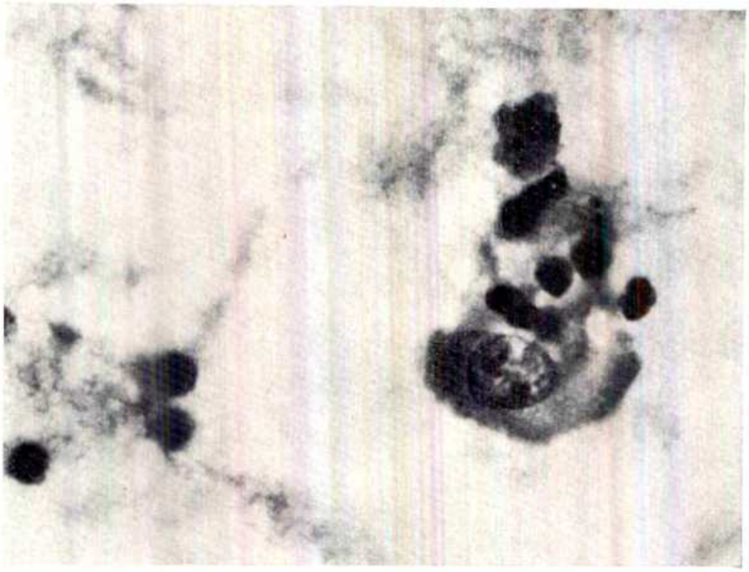

Fig. 2. Specimen 2. Large cell with coarsely clumped chromatin. The tattered cytoplasm is a common sign of degeneration and is also shown by some other cells which are out-of-focus polymorphs.

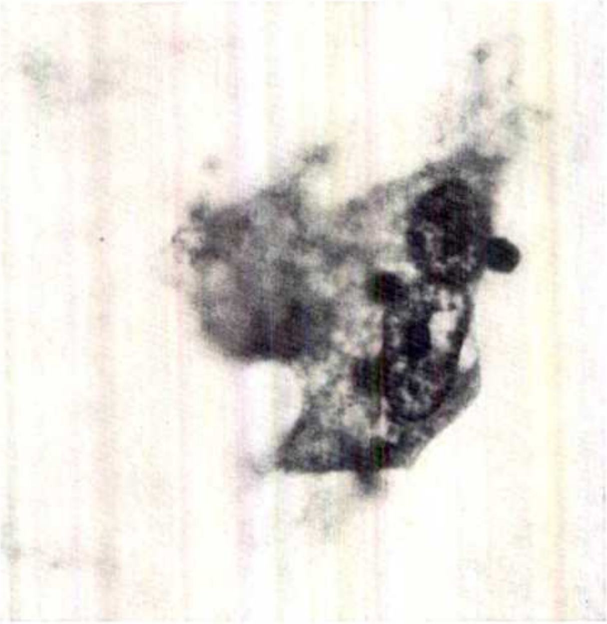

Fig. 3. Specimen 3. Large binucleate cell with ragged degenerate cytoplasm. Nuclei are relatively pale but show coarse chromatin and prominent nucleoli. The two spots in the cytoplasm are underlying polymorphs.

Discussion

In this study, as in a previous one (Cowen, 1971), the criteria used to diagnose malignant cells were anisocytosis (particularly large bizarre cells), pleomorphism, variation in nuclear size, increase of nuclear-cytoplasmic ratio, nuclear hyperchromatism and coarse clumping of chromatin. Vesicular nuclei are also compatible with a diagnosis of malignancy in the presence of some of the

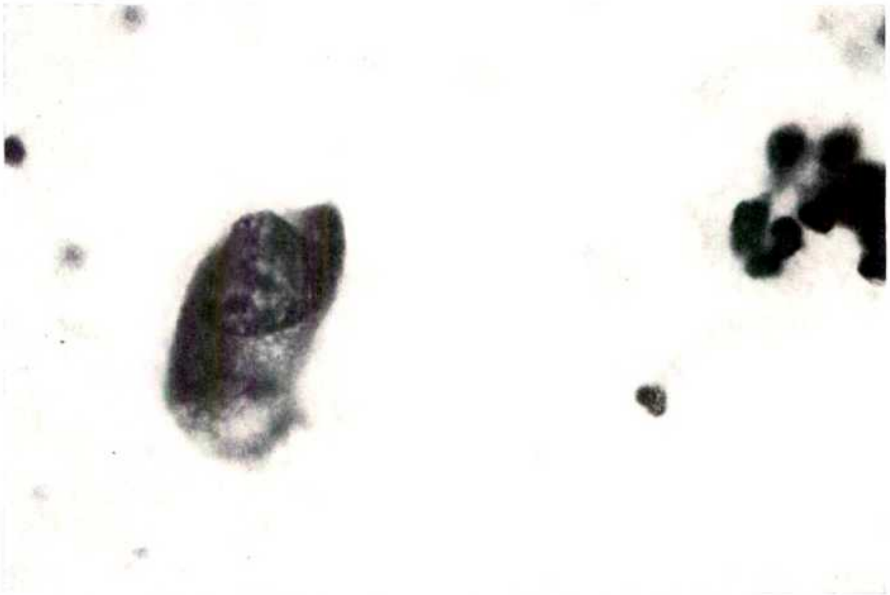

Fig. 4. Specimen 3. Large cell with clumped chromatin in nucleus. Compare size with out-of-focus tri-lobed polymorph.

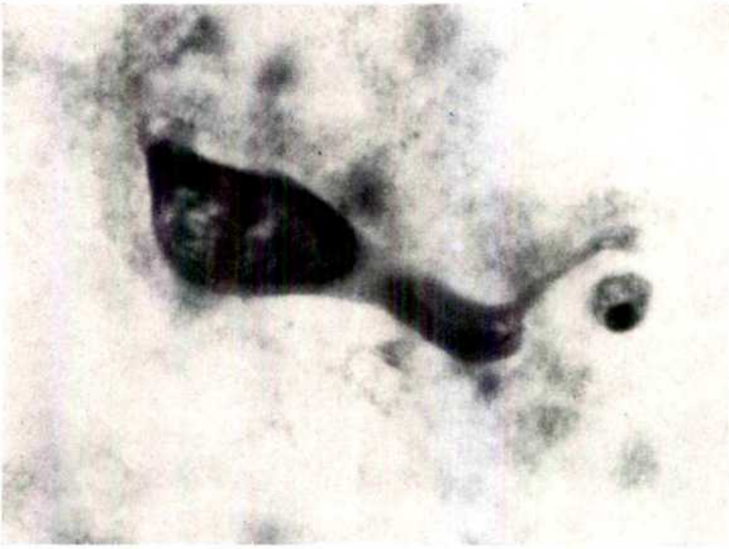

Fig. 5. Specimen 3. Very large bizarre cell with coarse irregular chromatin. The small cell is probably a histiocyte whose vacuolated cytoplasm merely signifies degeneration.

other criteria. Using these features, it is shown that bladders irradiated for cancer therapy may shed cells which appear to be malignant although no growth is present. The occurrence of such false positives has been described by several authors and in some cases it was suggested that irradiated benign cells could be distinguished from malignant ones. Seybolt (1960) admits that it is not always possible to attribute cellular atypia to radiotherapy, but says that in most cases there should be little confusion with malignancy. Specific features of radiation changes are not mentioned. Similarly, Goodman and Balfour (1964) report atypical cells resulting from radio-

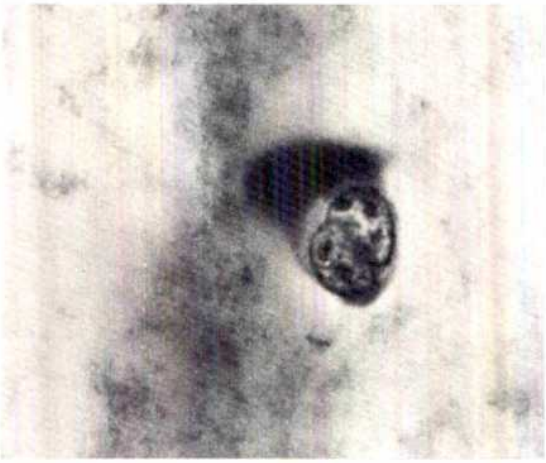

Fig. 6. Specimen 4. A rather large, binucleate cell with multiple nucleoli.

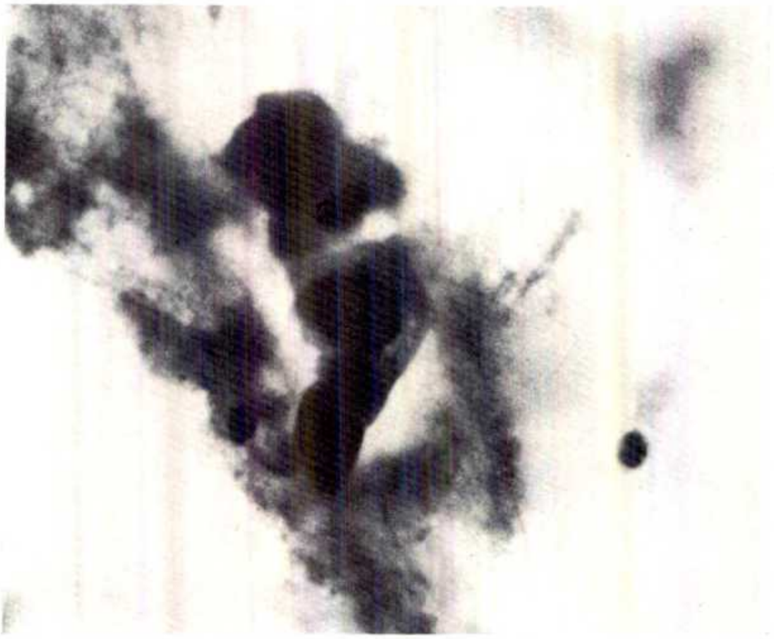

Fig. 7. Specimen 4. A clump showing pleomorphism, anisocytosis, hyperchromatism and a large nuclear-cytoplasmic ratio in at least two of the cells.

therapy without indicating how they may be recognised from malignant cells. Koss (1968, p. 413) does specify enlargement of cells, blown-up nuclei, pyknosis, karyorrhexis, and cytoplasmic eosinophilia and vacuolation but clearly states that these features are still liable to pose a diagnostic problem, concluding "... it appears wise to withhold diagnostic judgement in the presence of radiation changes until clear-cut evidence of cancer is obtained". Some of these features were seen in the present studies but, apart from cellular enlargement, they are all considered to be degenerative and liable to occur in any kind of cell—neoplastic, irradiated or normal. Esposti *et al.* (1970) agree with Koss (1968, p. 413) that caution should be exercised but claim that cytological diagnosis of a growth following radiotherapy is feasible in most cases that show clinical

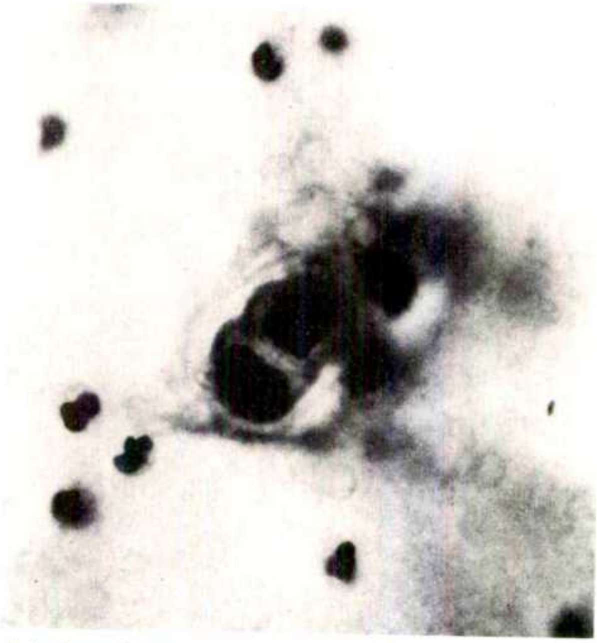

Fig. 8. Specimen 6. A clump showing similar features to the preceding but from a different patient.

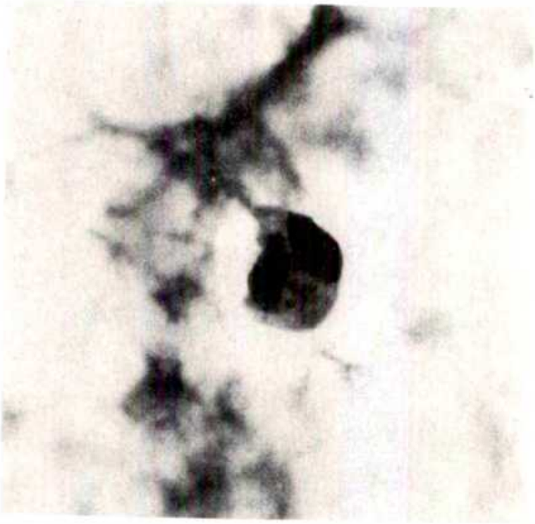

Fig. 9. Specimen 7. A bizarre, binucleate cell with dense nuclei.

signs of the growth. This feasibility is due to changes in degree rather than kind and the diagnosis is made on "pronounced cellular atypia" which accompanies growths at an advanced stage. Cytodiagnosis, however, is only of value in cases where new growths are undetectable by other means.

A more recent and very relevant study to shed light on this problem has been reported by Loveless (1973), who examined urines from patients receiving pelvic radiation. This was for bladder cancer and other pelvic tumours, and in the latter group the possibility of malignant urothelial cells appearing in the urine was remote. Cellular enlargement was considered to be the

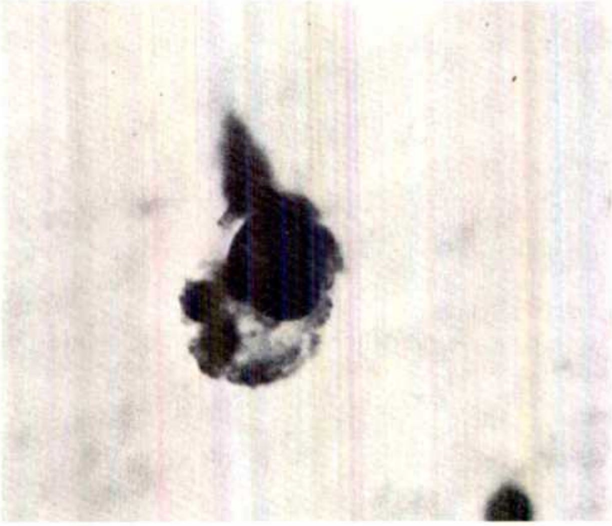

Fig. 10. Specimen 8. A large cell with large hyperchromic nucleus and vacuolated cytoplasm, which has phagocytosed two polymorphs (out of focus in the photograph but quite recognisable under the microscope).

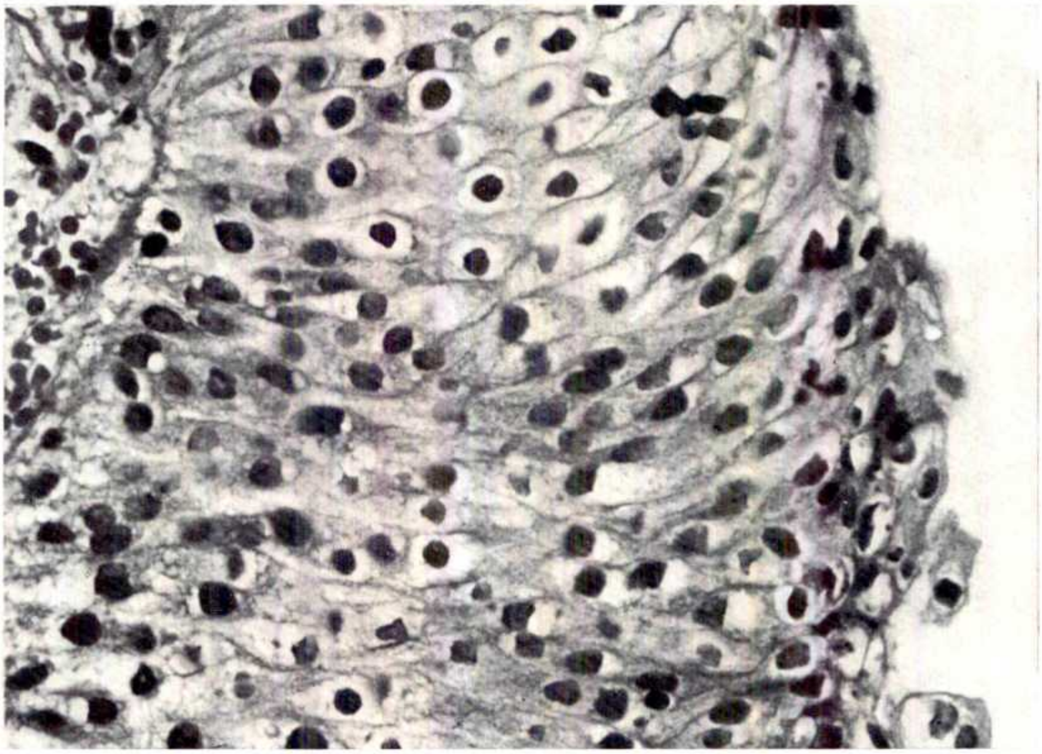

Fig. 11. Histology of bladder epithelium biopsy from patient 7. Nuclear hyperchromatism and increase in cell and nuclear size mainly at lower left (× 660).

most reliable criterion of radiation effect but this is too frequently seen in malignant cells in our studies to make it a valuable distinguishing feature in any single urine specimen. Other radiation changes mentioned are multinucleation, nuclear enlargement, polychromasia and cytoplasmic vacuolation. We find the first of these in normal, non-neoplastic cells and the last, as mentioned above, in any degenerate cells. Polychromasia (by Papanicolaou staining) is not seen here since we stain with haematoxylin and eosin, and nuclear enlargement (which results in an increased nuclear-cytoplasmic ratio) is a feature of malignancy. The criteria of malignancy in that study are essentially the same as used here.

Although relevant histological material was scanty in this study, the irradiation changes seen in the epithelia of the available biopsies were quite consistent with the features of the exfoliated cells which appeared to be malignant.

On review of the above literature together with our findings, we feel that it is impossible to state with any useful degree of certainty whether any atypical or bizarre cells seen in urine indicate a neoplastic origin, or whether they are due to the irradiation of non-neoplastic epithelial cells. The situation is similar to that in the case of the cervix uteri where "The differential diagnosis between benign and malignant cells after irradiation is often impossible" (Wachtel, 1964, p. 183). Each case must, of course, be dealt with on its own merits and if, for example, large numbers of very bizarre cells appear 2 years after irradiation and if there has been an interim period when cytological appearances were normal, then it is reasonable to suggest most strongly the possibility of a recurrence. If a cytodiagnosis service is to be useful, it is therefore essential that the cytologist be informed whether (and when) previous radiotherapy has been given to the patient. It should be pointed out that although in this survey only 9 out of 692 positive or suspect reports were found to be false due to radiotherapy, there must have been more, since we are not always informed about previous irradiation when a specimen is received.

Summary

Results from a urological cytodiagnosis service indicate that it is not possible to distinguish with any degree of certainty malignant from non-malignant irradiated urothelial cells in urine.

It is stressed, therefore, that when urine specimens are sent for cytological examination, details of any previous irradiation should be given to the cytologist.

The author wishes to acknowledge his appreciation of the photographic assistance given by Mr Stephen Toms and the assiduous service of the various cytology technicians who prepared the specimens.

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Carcinoma of the Bladder complicating Cyclophosphamide Therapy

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Cyclophosphamide is an alkylating agent which has been used extensively in the treatment of malignant disease, more especially for malignant lymphomas, for some 15 years. It has been recognised since its introduction that it may cause a severe haemorrhagic cystitis (Rubin and Rubin, 1966) and more recently widespread interstitial fibrosis between the muscle bundles of the bladder has also been described following its use (Johnson and Meadows, 1971). The clinical details of 2 cases of bladder carcinoma in patients on cyclophosphamide treatment were reported by Worth in 1971. Bladder tumours have not yet been described in experimental animals treated with this drug although Tokuoka (1965) has produced tumours elsewhere in mice following repeated small doses of cyclophosphamide. This paper documents 2 patients dying from carcinoma of bladder having previously had long-term chemotherapy with cyclophosphamide for malignant lymphoma.

Case 1

Clinical Details

J. J., a female, presented with cervical lymphadenopathy at the age of 50. Excision biopsy of a cervical lymph node showed the features of Hodgkin's disease of the nodular sclerosing type, and a course of radiotherapy was given to the mediastinum and left side of the neck, following which she remained well for 9 years. She then began to lose weight and the liver became enlarged on clinical examination. Treatment with cyclophosphamide was commenced and continued intermittently over the following 6 years, the dosage varying according to the peripheral blood picture. Over this time the patient received a total of 200 g of cyclophosphamide.

Haematuria then developed, occurring intermittently once or twice a week at the outset. A diagnosis of haemorrhagic cystitis following cyclophosphamide therapy was made and the offending drug discontinued. Over the next 2 months anorexia and lassitude developed and the patient became pyrexic. A chest X-ray revealed multiple ill-defined opacities in the right lung field and a lymphogram showed filling defects in the right para-aortic lymph nodes. A diagnosis of recrudescence of Hodgkin's disease was made and three courses of M.O.P.P. (a combination therapy comprising mustine, vincristine, procarbazine and prednisolone) were given over the next 2 months. However, the haematuria persisted and she was referred to the urology department. At the initial cystoscopy a 4 × 2 cm papilliferous tumour on the right wall of the bladder was seen. Intravenous urography at this time showed normal upper urinary tracts and slight irregularity of the bladder wall on the right. At a repeat cystoscopy 6 weeks later this tumour had grown considerably in size. The patient required repeated blood transfusions and finally developed pneumonia and died.

Pathology

A biopsy of the bladder taken at the time of the first cystoscopy showed a solid, poorly differentiated (Grade III) transitional cell carcinoma infiltrating muscle. Some tumour cells had clear cytoplasm which was demonstrated to be due to glycogen and other areas showed definite squamous differentiation (Fig. 1). A portion of the biopsy was necrotic and there were foci of calcification.

At autopsy the entire bladder mucosa was intensely haemorrhagic and there was a 6 cm diameter necrotic tumour arising from, and penetrating, the right wall of the bladder. There was no adherence to adjacent structures. Histology revealed tumour identical to that seen in the biopsy; tumour extended through all layers of the bladder musculature and was present in lymphatic vessels (Fig. 2). Other features in the bladder indicative of cyclophosphamide cystitis were widespread interstitial fibrosis, telangiectasia of vessels of the lamina propria and squamous metaplasia of urothelium of the trigone (Fig. 2). Metastases of tumour similar to that in the bladder were seen in the

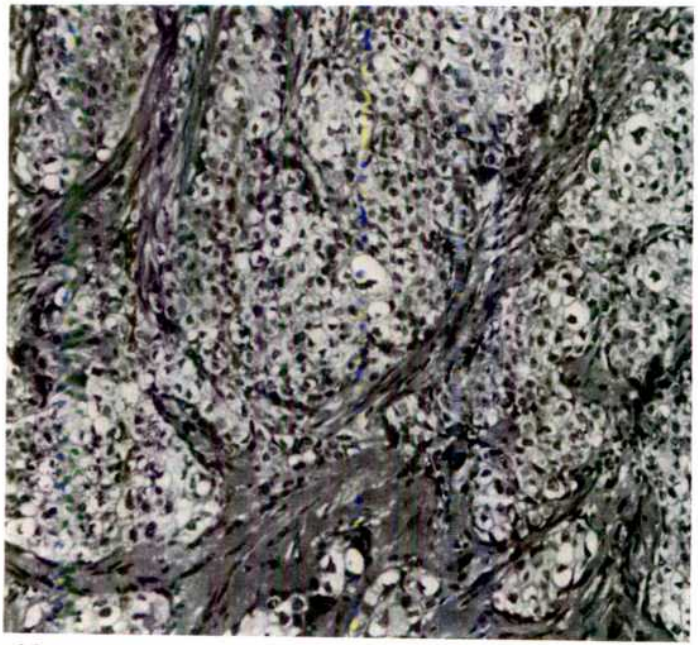

Fig. 1. Bladder biopsy of Case 1, showing solid Grade III transitional cell carcinoma with clear cytoplasm in some tumour cells. (Haematoxylin and eosin × 150.)

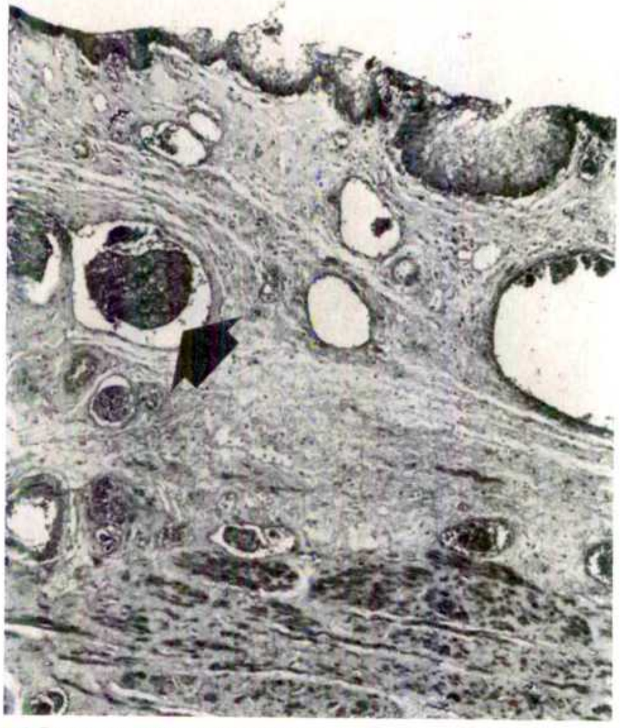

Fig. 2. Trigone of bladder of Case 1 at autopsy. Note telangiectatic vessels of lamina propria, squamous metaplasia of urothelium, interstitial fibrosis of muscularis and tumour in lymphatics (arrow). (Haematoxylin and eosin × 60.)

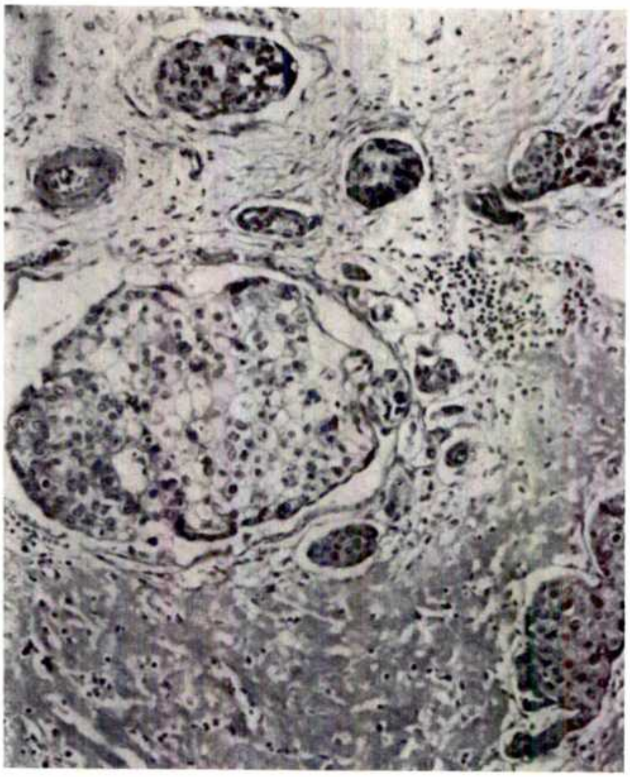

Fig. 3. Para-aortic lymph node from Case 1. Replacement of lymphoid tissue by acellular collagenous tissue and transitional cell carcinoma permeating sinuses. (Haematoxylin and eosin × 250.)

iliac and para-aortic lymph nodes, liver and lungs. No evidence of Hodgkin's disease was found although the para-aortic nodes were almost entirely replaced by dense fibrous tissue with metastatic tumour restricted almost completely to the subcapsular sinus (Fig. 3).

The kidneys (left 120 g, right 95 g) and ureters showed no macroscopic abnormality; in particular, no dilatation of the collecting system was seen. Histological sections of the kidneys showed no significant abnormalities.

Case 2

Clinical Details

M. R., a female, presented at the age of 61 with a swollen right leg due to deep vein thrombosis. Enlarged axillary lymph nodes were found on general examination and a biopsy of one of these showed a follicular malignant lymphoma of lymphocytic type. Several intravenous urograms were performed and all showed delayed excretion of contrast medium on the right with dilatation of both calyces and ureter on that side, the latter appearing to be obstructed at the level of the pelvic brim. The bladder outline was normal and the obstruction was considered to be due to enlarged lymph nodes. She was treated initially by four intravenous doses of vincristine and by radiotherapy to right groin and pelvis. Over the next 5 years she was treated intermittently with cyclophosphamide, the dosage varying with her peripheral blood count. She received over 100 g during this period. Whilst being treated she developed haematuria, frequency, dysuria and abdominal pain. This was thought to be due to cyclophosphamide cystitis, the drug was withdrawn and she was treated symptomatically for 3 months before being referred to the urologists. A further intravenous urogram showed that the right kidney had decreased in size (9·8 cm in length having been 11·5 cm 5 years previously) with a distended but normal calyceal pattern. The left collecting system and both ureters were normal but there was an indefinite impression over the left inferior border of the bladder. A course of radiotherapy was given to the bladder, but soon after this she developed oliguria. A further urogram showed no filling on the left side, dilatation of calyces and ureter on the right and a fixed, poorly emptying bladder. At laparotomy the tumour was inoperable due to local spread and metastasis to para-aortic lymph nodes. She died of uraemia shortly afterwards.

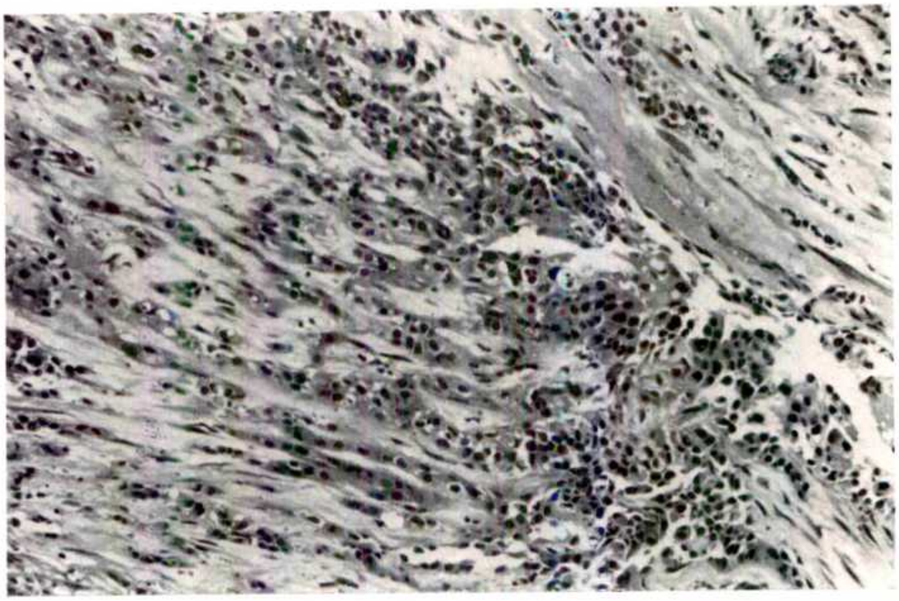

Fig. 4. Bladder biopsy of Case 2, showing infiltration of muscle by columns of solid Grade III transitional cell carcinoma. (Haematoxylin and eosin × 150.)

Pathology

Only a bladder biopsy was available for study. It showed an infiltrating (solid) poorly differentiated (Grade III) transitional cell carcinoma (Fig. 4). No squamoid differentiation was seen and approximately half the biopsy was completely necrotic. No bladder tissue was present to assess the presence of cyclophosphamide cystitis.

Comment

The occurrence of bladder tumour in 2 patients with cyclophosphamide cystitis was previously described by Worth in 1971. As in this report, his patients had lymphomas treated for long periods with cyclophosphamide.

Urological complications of cyclophosphamide are frequent (Watson and Notley, 1973) and cystitis is the most common. Breakdown products of the drug are responsible for the inflammation (Phillips *et al.*, 1961) which on microscopy is characterised by oedema of the bladder wall, uneven cellular enlargement with irregular hyperchromatic nuclei, infiltration with polymorphonuclear leukocytes and submucosal haemorrhages from dilated thin-walled blood vessels (Fontana-Donatelli, and Pasquinucci, 1962). These features of cyclophosphamide cystitis were found in the bladder at autopsy in Case 1, and in addition there was widespread interstitial fibrosis as described by Johnson and Meadows (1971) in 20% of their cases.

Development of bladder tumour in patients with cyclophosphamide cystitis may result from the fortuitous association of two common diseases. Bladder tumours are common and in a retrospective study of 444 patients with gynaecological tumours treated with cyclophosphamide 10% developed overt cystitis and 10 died from causes related to the cystitis (Spechter *et al.*, 1965). However, chronic irritation is associated with tumour induction and atypical cells have been described in urine from patients taking cyclophosphamide (Forni, Koss and Geller, 1964). Koss (1967) subsequently produced papillary hyperplasia of bladder epithelium in rats taking cyclophosphamide.

There is considerable evidence that the immune system is implicated in tumour destruction (Foley, 1953; Prehn and Main, 1957) but disagreement exists as to the relative roles of immunologically competent lymphocyte and lymphocyte-like cells, cytotoxic antibodies and macrophages in mediation of this effect. Each may predominate in defined circumstances.

Cyclophosphamide depresses cell mediated immunity, for it prolongs survival of skin allografts in mice (Medawar, 1969) and renal allografts in men (Starzl *et al.*, 1972), but its effects on humoral immunity are greater. Lymph nodes of animals given the drug show atrophy of lymph follicles, germinal centres and cortico-medullary junctions, which are areas associated with humoral immunity whereas paracortical areas, responsible for cell mediated immunity, were less affected (Turk and Poulter, 1972). All immunosuppressive agents, including cyclophosphamide, have no direct effect on macrophages but they may impair their effects by inhibiting division (Berenbaum, 1967). Cyclophosphamide, therefore, suppresses several arms of the immune response but the 2 patients reported here and those described by Worth (1971) received external irradiation and other cytotoxic drugs which also suppress immunity (Lance, 1972).

Lymphomas themselves may depress cell mediated immunity for patients with these diseases have prolonged allograft survival (Good *et al.*, 1962) and anergy (Lamb *et al.*, 1962). They are especially susceptible to tuberculosis, viral and fungal infections but humoral immunity is normal (Miller, 1962). The mechanisms of these abnormalities are not clear and interpretation is difficult because many patients also receive treatment with cytotoxic drugs.

Immunological reactivity of the patients described, who developed bladder cancer whilst taking cyclophosphamide, could result from any of the mechanisms described but immunosuppression alone is not associated with increased numbers of tumours (Nehlsen, 1971). However, immunosuppressed animals exposed to oncogenic viruses (Nehlsen, 1971), chemicals (Balner and Dersjant, 1969) or excess antigen have a high incidence of tumours. Goldman and Warner (1970) found cytomegalic virus in the transitional epithelium of a patient with haemorrhagic cystitis who was taking cyclophosphamide and many cytotoxic agents may be oncogenic (by irritation) and immunosuppressive (Penn and Starzl, 1972).

The development of a bladder tumour in a patient with cyclophosphamide cystitis may be easily overlooked unless cystoscopy and biopsy are performed.

Summary

Two patients with cyclophosphamide induced cystitis and co-existent bladder tumour are described. Possible mechanisms for these associated diseases are discussed and the difficulty of diagnosing bladder tumour in patients with haemorrhagic cystitis is stressed.

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Non-parasitic Chyluria (presenting with Urinary Retention)

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Chyluria was recognised by Hippocrates, Galen and Pheophile. Pecquet in 1653 attempted to give a detailed description of the lymphatic system. It was not until 1741 that Morgagni first associated chyluria with abnormalities of the lymphatic circulation. It was not until the advent of retrograde pyelography and later percutaneous lymphangiography that abnormal connections between the lymphatic and urinary systems were demonstrated in the living subject. Pyelolymphatic reflux was demonstrated by Wood during retrograde pyelography in 1929 though it was as recently as 1963 that Kittredge *et al.* outlined these communications by lymphangiography.

Chyluria is broadly classified into two main aetiological groups: (1) parasitic or tropical and (2) non-parasitic. Non-parasitic chyluria is rare. Clinically it presents as a metabolic disturbance due to loss of fat (Mogg and Jones, 1971), or more rarely with obstructive symptoms. Two cases of this latter group are described in adult males presenting with recurrent attacks of retention of urine.

Case I

In May 1964, a 25-year-old furniture remover presented at the Manchester Royal Infirmary complaining of the passage of white milky urine. He first noticed this in 1959, and again in 1960 on isolated occasions. At the time of presentation it had been present continually for several weeks, most marked on rising in the morning. On several occasions he had experienced difficulty in micturating and complained of a continuous dull aching pain in the right loin.

There was no past medical history of note, nor any family history of similar complaints. The only time he had left his home town in Derbyshire was for a period of a few months whilst stationed on Army duty in the Mediterranean during 1953.

The patient was healthy in appearance and there were no abnormalities on physical examination. His urine was obviously "milky" and contained 740 mg of fatty acid per 100 ml, 8·9 g in a 24-hour specimen. Haemoglobin, blood urea, liver function tests, serum albumin and serum electrolytes were all normal. The urine was normal apart from the presence of chyle, with the exception of one sample which contained 50 red blood cells per high power field. Radiology of the chest and abdomen together with excretion pyelography were all within normal limits. Cystoscopy revealed milky urine coming through the right uretero-vesical orifice. Bilateral retrograde pyelography demonstrated incomplete filling of the right upper and middle pole calyces, but no other abnormality. Bilateral percutaneous lymphangiography outlined an abnormal connection between the para-aortic lymph channels and the right renal lymphatics (Fig. 1). A number of widely dilated lymph vessels in the hilum of the right kidney were demonstrated. The thoracic duct was well outlined, indicating that no obstruction existed to the normal cranial flow of chyle (Fig. 2). The appearances represented a right lymphatico-renal fistula.

Symptoms resolved spontaneously but in September 1965 the patient was re-admitted after some months of continuous chyluria. The right kidney was explored and large lymphatic vessels exposed, particularly around the right renal vein anteriorly. These vessels were mobilised and divided. Postoperatively the patient was asymptomatic until January 1969, when he had slight recurrence of chyluria which disappeared spontaneously following hospital admission. The patient is now on a low fat diet and has remained free of symptoms to date.

Case II

A 34-year-old English male presented at the Manchester Royal Infirmary in January 1966 complaining of the passage of "milky" urine accompanied by suprapubic discomfort, an aching pain in the right renal angle and some difficulty in passing urine. His symptoms began whilst he was a naval rating in Malta in 1953. Investigation in

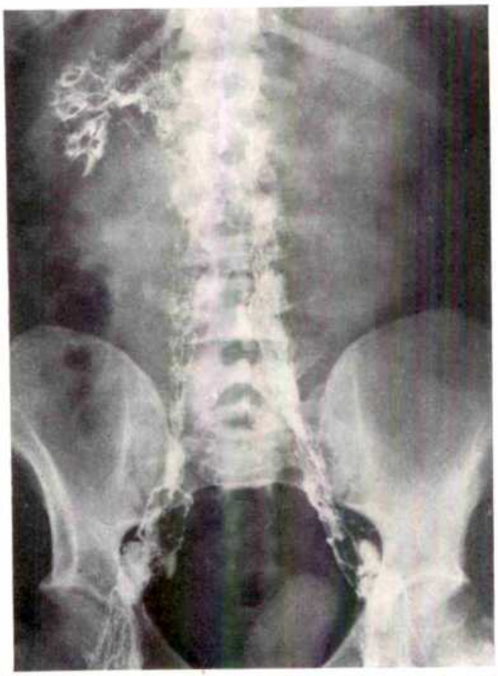

Fig. 1. Case I. Lymphangiography. Abnormal connection between para-aortic lymph channels and right renal lymphatics.

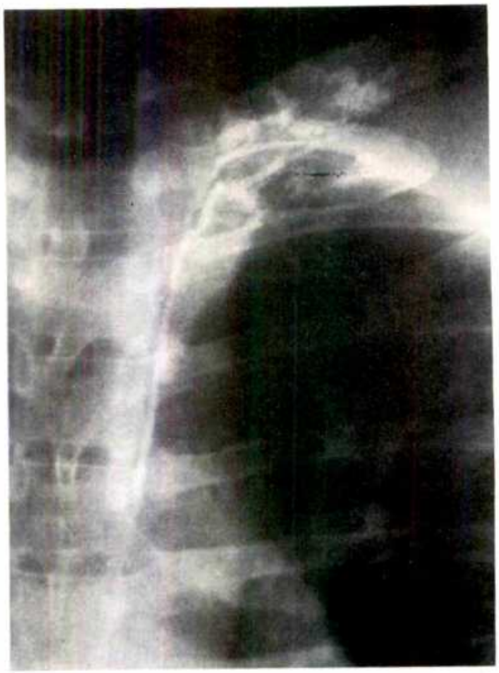

Fig. 2. Case I. Lymphangiography. Normal thoracic duct.

Malta at that time showed no abnormality apart from the occasional demonstration of fat in the urine. His symptoms recurred 2 years later when it was noticed that his urine was heavily loaded with fat and albumin and contained some red blood cells, but no pus cells were found. The chyluria cleared spontaneously after a few days.

Later that year he developed a urinary tract infection, the organism being *Staph. pyogenes*. Excretion and retrograde pyelography were normal and the infection responded to antibiotic therapy. He was again investigated in 1956, following several attacks of incomplete urinary retention culminating in acute retention which required catheterisation. The pain which accompanied the attacks on these occasions was in both loins and both iliac fossae. The possibility that the chyluria was associated with filariasis was considered at this time, but microbiological investigation of nocturnal specimens failed to reveal any abnormality. The patient had never visited an area where this condition is endemic.

He was at this stage placed on a low fat diet, whereupon the chyluria again disappeared. The patient felt that the exacerbations of colic and retention seemed less frequent and severe, and also that the quantity of lymph in his urine during the exacerbations was reduced whilst adhering to the diet.

Retrograde pyelography, performed in 1959, demonstrated connections between the right renal pelvis and the abdominal lymphatics (Fig. 3).

In 1964 lymphangiography was performed. In addition to abnormal lymphatic communications to both kidneys, more marked on the right side, an extensive lymphangiomatous malformation was demonstrated in the pelvis with lymphatic connections extending over the posterior abdominal wall Contrast was demonstrated in the bladder at an early stage of the examination (Fig. 4). The thoracic duct was well outlined and showed no evidence of obstruction (Fig. 5).

Many examinations were made on the urine. When it was cloudy, fat could always be demonstrated. Sudan III dye was taken with a fatty meal and the pink colour of the next specimen of urine was obvious. Estimation of the quantity of fat in the urine gave various readings; those on 2 consecutive days in 1963 were 120 mg per 100 ml in 1,950 ml of urine, *i.e.* 2·34 g per day, and 207 mg per 100 ml in 1,800 ml of urine, 4·7 g per day. Protein was always present along with fat, and on standing at room temperature clots formed within the urine. Red blood corpuscles and polymorphonucleocytes were often demonstrated and on a few occasions organisms were found, mainly *E. coli* and *Staph. pyogenes*.

Blood urea, full blood count, erythrocyte sedimentation rate, serum proteins, and liver function tests were checked on many occasions and always were within normal limits The eosinophil count was never greater than 300/cu.m. Numerous nocturnal smears for microfilaria were negative.

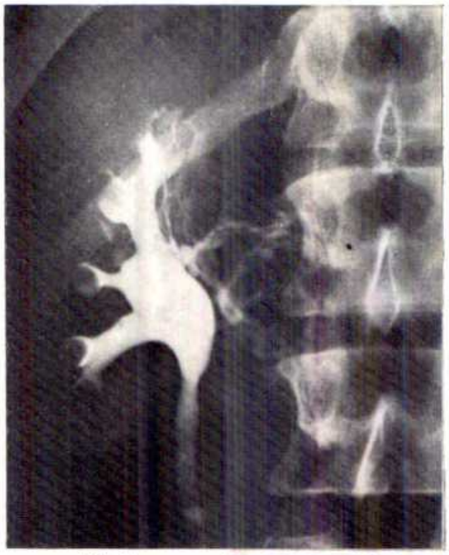
Fig. 3

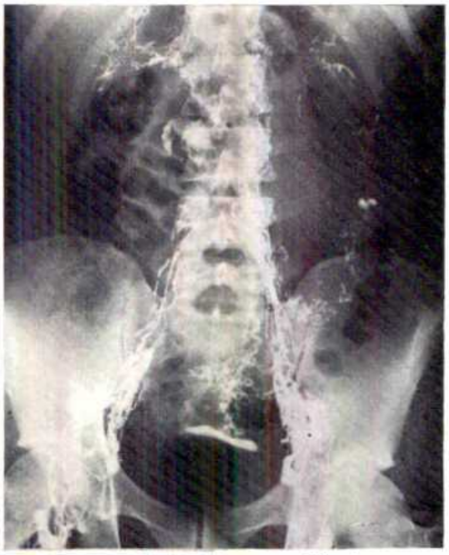
Fig. 4

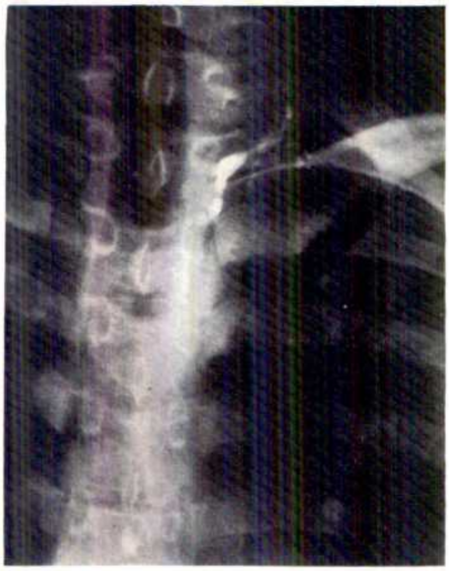
Fig. 5

Fig. 3. Case II. Right retrograde pyelography. Abnormal connections between para-aortic lymph channels and right renal lymphatics.

Fig. 4. Case II. Lymphangiography. Abnormal lymphatic communications to both kidneys. Lymphangiomatous malformation in the pelvis. Contrast medium in the bladder.

Fig. 5. Case II. Lymphangiography. Normal thoracic duct.

The continued attacks of colic and retention inconvenienced the patient greatly and he was therefore admitted with a view to surgical exploration of both kidneys. On clinical examination at this time the only abnormality was some slight tenderness in the right renal angle and right hypochondrium.

At operation there were numerous large lymphatic channels surrounding the hilum of the right kidney and a mass of lymphatic tissue was seen at the junction of the right renal vein and inferior vena cava. On the left a leash of lymphatics was present, extending from the kidney across to the cysterna chyli. All the dilated lymphatic trunks were ligated and divided. Ths patient's postoperative condition was good. He has now remained free from symptoms for almost 10 years.

Discussion

Prout (1840) proposed the first theory to explain the aetiology of chyluria postulating that fat was secreted from the blood stream into the urine. This theory substantiated the findings that increased intake of fat increased the chyluria but failed to explain the effect of posture and exercise on chyluria and the rarity of the condition. Golding Bird (1843) finally discounted the secretory theory by showing that the fat in chylous urine was in the form of molecular particles rather than globules.

In 1862 Carter suggested that chyluria might be caused by rupture of a lymphatic varix into the urinary tract. Ackermann in the following year explained the development of chyluria on the basis of a mechanical obstruction of the lymphatics between the bowel and the thoracic duct. The obstruction would produce an increase in intralymphatic pressure, lymphangiectasia, valvular incompetence and retrograde flow of chyle resulting in a lymphatico-renal shunt.

Rupture of lymphatic vessels into the kidney has been explained on the basis of a relative lack of supporting tissue elements in the renal parenchyma associated with its inadequate supply of collateral blood vessels (Ackermann, 1963). Fistulous openings and chylous reflux have been reported in the trigone by Pope (1909) and by Lazarus and Marks (1946).

In the embryo, lymphatic channels develop from primitive lymph sacs, 2 of which lie in the peri-renal area. The diffuse and dilated peri-renal lymphatics described in these 2 cases and demonstrated by lymphangiography may represent an abnormal or incomplete differentiation of these peri-renal lymph sacs. In favour of such a congenital abnormality is the absence of any evidence of obstruction to these lymphatics or to the thoracic duct. This suggests abnormal development in one or more of the primitive lymph sacs, the posterior lymph sacs in the region of the sacro-iliac joints are abnormal as well as the peri-renal sacs in Case II. It would appear not to be a generalised abnormality but perhaps a localised lymphatic malformation such as lymphangioma involving one or more of the primitive lymph sacs.

Clinical features

The disorder is usually unilateral, the left kidney being more frequently affected and symptoms are characteristically intermittent. Chyluria has been reported in an infant of 17 months by Brandenberg (1909), but most cases present in the second or third decade. Pain is a common symptom, presumably due to obstruction along the urinary tract and acute retention of urine is known to occur (Craig and Woodroffe, 1969). These features are presumably referrable to the viscosity of the urine from the chyle which formed "clots" in our 2 cases. More commonly there is general impairment of health with weight loss, debility or anaemia. Superimposed urinary tract infection is common (Yamauchi, 1945).

Treatment

A fat-free diet has a palliative effect on the exacerbations of symptoms and during an attack the effect may well be dramatic (Ray and Rao, 1939). Treatment based upon injection of sclerosing agents into the lymphatics or local diathermy of the fistula tends to be unsatisfactory (Mogg and Jones, 1971).

Visualisation of the lymphatics by percutaneous lymphangiography and the use of dyes such as Sudan III and methylene blue have enabled elaborate by-pass procedures to be carried out such as jugulo-thoracic duct anastomosis and anastomosis of a varicose lymphatic and the testicular or ovarian vein (Cockett and Goodwin, 1962). Surgical stripping of the renal pedicle lymphatics is the treatment of choice in most cases where surgery is necessary though in infective cases abnormal communications may recur.

Summary

Two cases of non-parasitic chyluria are presented each presenting with retention of urine.

Abnormal communications in both cases have been demonstrated lymphangiographically. The thoracic ducts were patent and there was no evidence of filariasis.

Surgical removal of the anomalous dilated lymphatics was carried out, the patients being symptom-free at 7 and 10 years.

The two cases seem to have lymphatic malformations which may be the basis of the disorder.

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Short Case Report

Occurrence of Vesical Calculus following Renal Transplantation

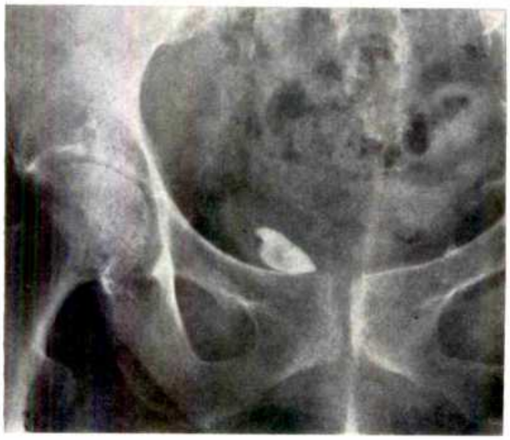
The development of a calculus at the site of ureteroneocystostomy after renal transplantation has not been previously reported to our knowledge. Below is described our experience with such a case.

Case Report

A 58-year-old woman with end-stage renal failure due to chronic glomerulonephritis began haemodialysis in August 1972. She had no history of urinary tract infections or urinary calculous disease. Complete urological investigation was normal except for bilaterally small kidneys commensurate with chronic glomerulonephritis. The serum calcium concentration was 9·2 mg/dl and the serum phosphorus concentration, 9·9 mg/dl. She underwent bilateral nephrectomy in September 1972 and received a living-related-donor renal allograft 6 weeks later. Transplantation was uncomplicated. The allograft ureter was reimplanted into the bladder, a submucosal tunnel and ureteral cuff technique being used, as previously described (DeWeerd, Woods and Leary, 1973).

All suture material used in the urinary tract was 4-0 chromic catgut. No splints were used. The Foley urethral catheter was removed on the 5th post-transplant day and voiding was normal. The serum creatinine concentration stabilised at 0·8 mg/dl. The urine was sterile throughout her hospital course. She was dismissed on the 10th postoperative day on a regimen of azathioprine (Imuran) 75 mg daily and prednisone 20 mg and 17·5 mg on alternate days.

Follow-up evaluations at 1 month and 6 months were normal. At the 12-month follow-up she stated that she had been "passing some gravel" in her urine 1 week previously. She had no other symptoms and urine culture was sterile. The renal allograft appeared normal on the excretory urogram. However, an irregularly oval density (1 by 2 cm) having a non-opaque centre was present in the bladder (Fig.). The serum concentrations of calcium and phosphorus were 10·7 and 3·2 mg/dl, respectively. Cystoscopy revealed a smooth yellow-white calculus (1 by 2 cm) tenuously attached to the site of the previous ureteroneocystostomy. The slender attachment of the calculus appeared to be at the site of the prior suture line uniting the posterior edge of the ureteral cuff to the bladder mucosa. The ureteral orifice itself appeared normal. Litholapaxy was performed and the patient was dismissed 3 days later.



Histological examination of the calcareous material removed showed a fibrous connective tissue nidus with a calcified outer surface correlating well with its radiographic appearance. Analysis of the calculus showed that it was composed of calcium phosphate.

Comment

We feel that the calculus resulted from dystrophic calcification of an ischaemic portion of the cuff of the allograft ureter. Isolated rejection of such a small portion of tissue seems highly unlikely, and there was no evidence of urinary infection. It seems most likely that the ureteroneocystostomy rendered a small area of ureteral mucosa ischaemic and that this resulted in calcification. Meticulous attention to detail in performing all aspects of renal allograft surgery should keep such complications to a minimum.

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Reference

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The Effect of an Antibacterial Drug on Urinary Calcium, Magnesium and Phosphorus Excretion in Patients with Neurogenic Bladder

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Infection of the urinary tract is a constant source of concern to the clinician in charge of patients with spinal cord injury. Long-term antibiotic therapy merely changes the resistance of the organisms. Hexamine, which decomposes into formaldehyde and ammonia at a pH of 5·5 or less, possesses broad spectrum antibacterial activity without inducing the development of resistant strains (Di Palma, 1971). G 500[1], a combination of hexamine with the acidifying agents methionine and mandelic acid, is used routinely at this Centre as a prophylactic both against the acquisition of urinary tract infections and against calculus formation (Guttmann and Frankel, 1966).

Another consequence of spinal cord injury is an increased urinary calcium excretion. This may continue for many months, resulting in osteoporosis and osteomalacia, and contributing to the danger of urinary stone formation (Abramson, 1948; Freeman, 1949). The administration of drugs which increase this process is obviously undesirable. The hypercalciuric effect of acids, or of ammonium chloride (Farquharson *et al.*, 1931), is seldom mentioned in textbooks of urology in the context of the treatment of infection by acidifying drugs. It was therefore decided to study the effect of G 500 on electrolyte excretion in paraplegic patients.

The first experiment was a short-term study in which G 500 was given for 7 days to 2 groups of patients. Those in the first group were studied about 6 weeks after injury. At this time the rate of loss of calcium from the body is maximal (Claus-Walker *et al.*, 1972; Burr and Walsh, 1974). The second group consisted of patients who had been paraplegic for more than a year, and in whom therefore the rate of loss of bone mineral should have been less.

The second experiment involved a longer-term study of patients who were receiving G 500 as part of their routine clinical management. The drug was stopped and appropriate antibiotic therapy was substituted when the urine became infected. After successful treatment of the infection, the antibiotic was stopped and therapy with G 500 recommenced. Thus it was possible to compare the effect of G 500 with that of the antibiotic treatment over a period of several months.

Patients and Methods

Experiment 1 (short-term). Group 1A consisted of patients with traumatic paraplegia of recent onset (Table 1a). Management of spinal fracture was by postural reduction (Frankel *et al.*, 1969). Urinary infections were treated by appropriate antibiotic therapy.

The patients in Group 1B had been paraplegic for at least 18 months (Table Ib). All had previously received G 500 for many months but this had been discontinued for at least a week prior to the study. They had been admitted for treatment of pressure sores (in 6) or for surgery (transurethral resection of bladder neck in 1). They were all confined to bed during the study.

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[1] G 500 Each tablet contains 250 mg hexamine mandelate and 250 mg methionine (Ward Blenkinsop Pharmaceuticals Ltd., Wembley, Middlesex).

Table Ia

Patients with Recent Injury to Spinal Cord

Patient	Age (years)	Spinal cord lesion	Associated injuries	Duration of cord lesion at commencement of study (weeks)	Intravenous pyelogram
1	16	L4 i	Head injury	6	Right hydronephrosis
2	18	T5 c	None	4	Normal
3	20	T4 c	Fracture	6	Normal
4	45	C7 i	None	6	Normal
5	22	T10 i	None	6	Normal
6	21	L2 i	Gun shot wound to buttock and left kidney	4	Right pelvis slightly dilated
7	34	T10 c	Abrasions	4	Normal
8	33	T6 c	Lacerations, concussion	6	Normal
9	17	T4 c	Fractured humerus and sternum	4	Normal
10	24	C6 c	Lacerations, fractured finger	5	Normal
11	18	T3 c	Lacerations, head injury	4	Normal
Mean	24·4			4·9	

C = cervical vertebra; T = thoracic vertebra; L = lumbar vertebra; c = complete lesion; i = incomplete lesion.

Table Ib

Patients with Spinal Cord Lesion of more than 1 Year's Duration

Patient	Age (years)	Spinal cord lesion	Duration of lesion (years)	Intravenous pyelogram	Creatinine clearance (ml/min)
12	16	T8 c	12	Normal	82
13	24	T4 c	5	Normal	—
14	45	T10 i	1½	Normal	63
15	35	T5 c	14	Slight blunting of calyces	120
16	55	C6 i	3	Pyelonephritic changes	83
17	59	T5 c	8	(Post mortem: small pyelonephrotic kidneys, gross amyloidosis)	—
18	60	T9 c	4	Normal	48
Mean	42·2		6·8		

From the patients in Groups 1A and 1B 24-hour collections of urine were obtained on the last 5 days of each of 3 consecutive 7-day periods. The first and third weeks served as control periods. The patients received G 500 throughout the second week. The dose was 8 tablets per day for Group 1A and 6 per day for Group 1B.

Experiment 2 (long-term). Group 2 consisted of patients with traumatic paraplegia of recent onset (Table II). Study commenced not earlier than 6 weeks after injury and continued for up to 3 months. Management was as described for Group 1A. The patients were given G 500 in a dose of

Table II

Patients with Recent Injury to Spinal Cord. Study commenced at 6 weeks

Patient	Age (years)	Spinal cord lesion	Dose of G 500	Associated injuries	Intravenous pyelogram
19	21	C5 i	8	None	Normal
20	40	C5 c	8	None	Normal
21	20	T5 c	16	Fractured clavicle; pneumothorax	Some blunting of calyces
22	18	C5 c	6	Bruises, fractured clavicle	Normal
23	36	T10 c	6	None	Normal
24	16	L1 i	6	None	Normal
25	15	C6 c	8	None	Normal
26	23	T4 c	6	Bruises	Normal
27	28	C6 c	8	None	Dilatation of lower left ureter
28	44	T9 c	8	None	Normal
29	25	T10 c	8	Lacerations	Normal
Mean	26·0				

6 to 16 tablets per day as part of their routine clinical management, but antibiotic therapy was substituted when there was urinary infection, as indicated by daily dip-slide examination. Three consecutive 24-hour specimens were obtained at 2-week intervals. Specimens collected less than 4 days after a change of treatment were rejected. The average time of administration of G 500 before specimen collection was 18·0 days, and the average duration of the control (antibiotic therapy) periods before specimen collection was 22·9 days.

All the patients studied were male, and they all received the normal ward diet throughout. The levels of the cord lesions were assessed clinically.

To each 24-hour specimen 50 ml 4 m hydrochloric acid was added. Sodium and potassium were determined by flame photometry, calcium and magnesium by atomic absorption spectrophotometry, and inorganic phosphate and creatinine by Auto-Analyser. The urine was collected using a condom urinal device in most cases, since few of the patients were catheterised, either continuously or intermittently, and their bladders were emptying automatically. It was therefore impossible to time accurately the beginning and end of each 24-hour collection. Only specimens that were at least approximately complete, as judged by the creatinine content, were accepted, and the ratios of calcium, magnesium, phosphate, sodium and potassium to creatinine were used for statistical analysis. The results for control and G 500 treatment periods were compared using Student's *t* test.

Results

Figure 1a shows the mean calcium results for the control and test periods for each patient in Group 1A. Four patients showed an increase in calcium excretion in response to G 500, 1 a decrease, and in the remaining 6 the change was not statistically significant. The mean calcium content of all the control specimens was 388 mg per g creatinine, compared with 426 mg/g for the test specimens, an increase of 10%, which was not significant ($P > 0{\cdot}05$).

Figure 1b shows the mean results of the calcium, magnesium and inorganic phosphate analyses for each patient in Group 1B. The mean calcium excretion increased in every patient while being given G 500, but this was significant in only one ($0{\cdot}05 > P > 0{\cdot}02$). For the group as a whole there was an increase of 20·5% ($0{\cdot}05 > P > 0{\cdot}02$) from a control value of 268 mg/g to 324 mg/g for the test specimens. The magnesium and phosphate results were variable and there was an overall fall in phosphate output from 902 to 817 mg/g ($0{\cdot}02 > P > 0{\cdot}01$).

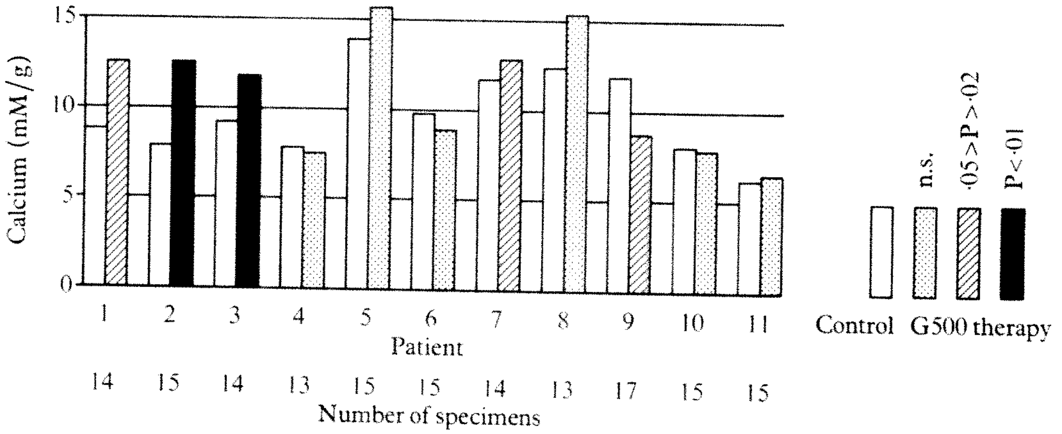

Fig. 1a. Urinary excretion of calcium (expressed as mM/g creatinine) in patients with recent spinal cord injury. Mean results for 24-hour urine collections during control periods compared with those obtained during G 500 therapy. Dosage: 8 tablets per day for 7 days.

Figure 2 shows the mean results for each patient studied in Experiment 2. There was an increase in calcium excretion in response to G 500 in all 11 patients, being significant in 6 ($P<0{\cdot}02$). For the group as a whole the increase was from 244 mg/g to 406 mg/g (64%—$P<0{\cdot}001$). Four patients had a significant increase in magnesium excretion and 4 an increase in phosphate excretion in response to G 500 therapy. For the group there was an increase in magnesium output of 37% (from 80 to 110 mg/g—$P<0{\cdot}001$) and in phosphate output of 30% (from 610 to 802 mg/g—$P<0{\cdot}001$).

In no group were there consistent changes in sodium or potassium excretion.

Discussion

Creatinine excretion was unrelated to drug therapy, and since only approximate 24-hour collections were analysed it was assumed that differences in the diurnal rhythms of electrolytes and creatinine would not affect the results. The procedure of expressing the excretion of calcium, etc., in terms of creatinine was therefore considered to be valid.

Changes in electrolyte excretion with time must be taken into account when studying the effects of drugs on metabolism during the first few months following spinal cord injury. Rapid changes occur in the urinary output of calcium and creatinine during the first 4 weeks, and in potassium, magnesium and inorganic phosphate during the first 6 weeks of paraplegia (Burr and Walsh, 1974). In addition, there is considerable day-to-day variation in calcium excretion. Together, these factors probably account for the variation in the response of different patients to G 500 therapy observed in Group 1A.

Pyelonephritis is common in patients, such as those in Group 1B, with paraplegia of long-standing, and is frequently associated with renal tubular acidosis (Cochrane *et al.*, 1968). In these circumstances there might be an increased response to G 500 therapy, due to impaired ability to eliminate an acid load. Pyelonephritis was present in 2 patients and possible in all (Table Ib). An ammonium chloride loading test was not attempted because infection of the urine invalidates pH measurements (Doggart and Silver, 1966). Thus the difference between the results obtained in Groups 1A and 1B may have been due to the presence of renal impairment in Group 1B.

Greater confidence can be attached to the findings when they are compared with the results of similar experiments using an anabolic steroid instead of G 500. Thus, in an experiment identical in design to Experiment 1A, oxymetholone[1] in a dose of 10 mg at 6.00 hours daily brought about

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[1] Oxymetholone: 17β-hydroxy-2-hydroxymethylene-17α-methylandrostan-3-one. "Anapolon"-Syntex Pharmaceuticals Ltd., Maidenhead, Berkshire.

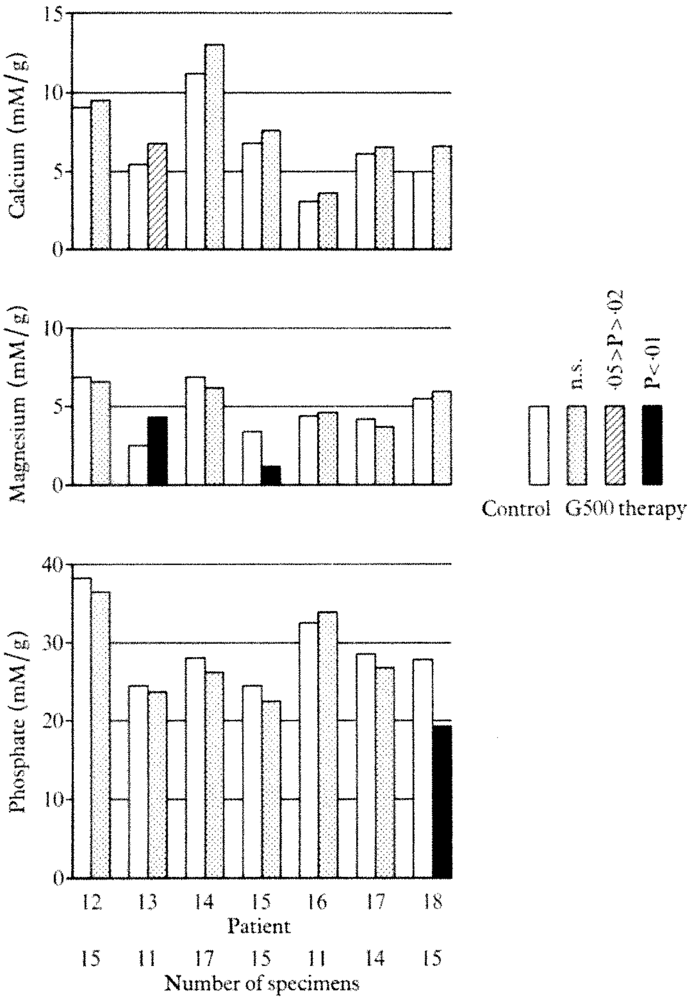

Fig. 1b. Urinary excretion of calcium, magnesium and inorganic phosphate (expressed as ratios to creatinine) in patients with spinal cord lesion of more than 12 months' duration. Mean results for 24-hour collections during control periods compared with those obtained during G 500 therapy. Dosage: 6 tablets per day for 7 days.

a 23% reduction in urinary calcium in a group of 5 paraplegic patients (Moore Ede and Burr, 1973). Similarly, in a long-term experiment, administration of the same steroid to a group of 10 patients resulted in a fall in mean urinary calcium from 402 mg/g to 378 mg/g (not significant) (Fig. 3). The corresponding figures for magnesium were 86 and 83 mg/g, and for phosphate 762 and 684 mg/g (n.s.). Thus the magnitude of the effect produced by G 500 increased with the duration of administration, whereas the opposite was true of oxymetholone.

Ammonium chloride loading, whether acute or chronic, leads to an increase in the urinary excretion of calcium, magnesium and phosphate (Farquharson *et al.*, 1931; Martin and Jones, 1961; Lavan, 1969). In acidosis the plasma diffusible calcium concentration rises leading to an increase in the filtered load of calcium at the glomerulus (Williamson and Freeman, 1957). In addition, the renal tubular reabsorption of calcium is diminished (Lemann, Litzow and Lennon, 1967; Stacey and Wilson, 1970). In chronic uraemic acidosis the bone carbonate content falls linearly over a period of months (Pellegrino and Biltz, 1965) and it is probable that the increased amounts of calcium, magnesium and phosphate found in the urine of many acidotic subjects are

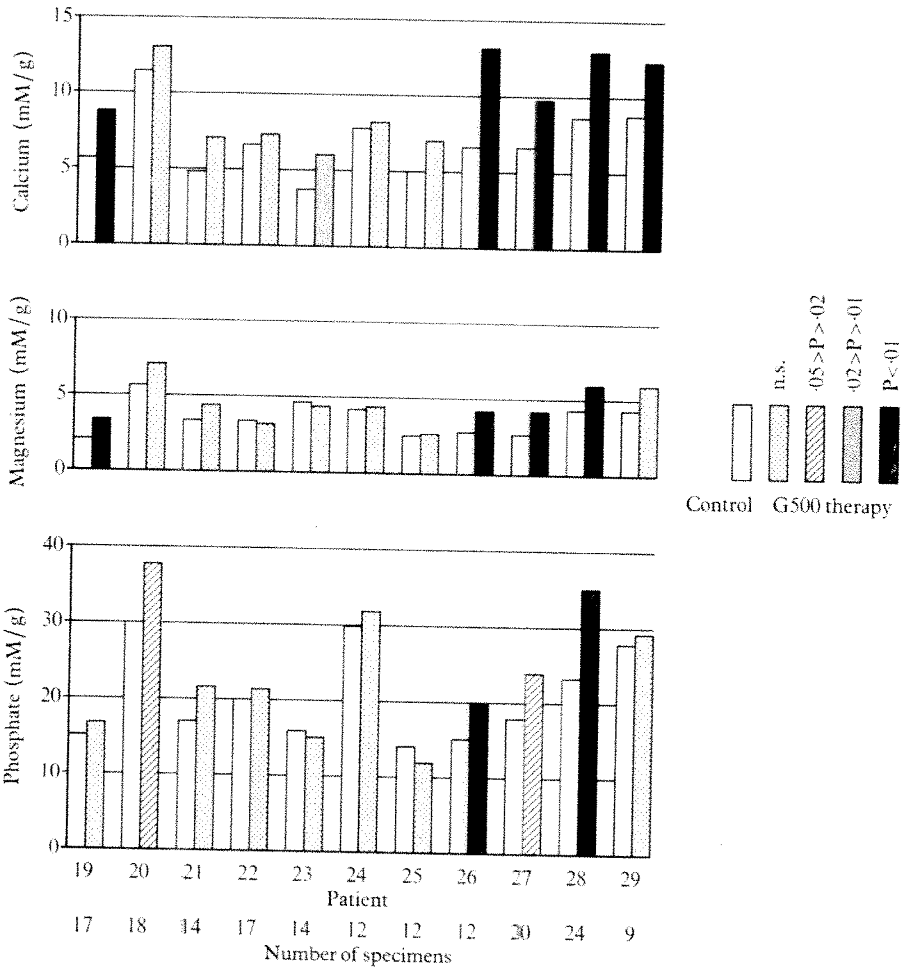

Fig. 2. Urinary excretion of calcium, magnesium and inorganic phosphate (expressed as ratios to creatinine) in patients with recent spinal cord injury. Mean results for 24-hour urine collections during G 500 therapy, from 6 weeks to 3 months after injury. Dosage: 6 to 16 tablets per day.

derived from bone. There have been few reports of studies with other acidifying drugs. Murphy and Zelman (1965) found that the administration of 6 to 12 g ascorbic acid daily lowered the urinary pH and raised the urinary calcium output by 60 to 80 mg/day. The present results indicate that G 500 is capable of producing a similar effect.

A high fluid intake will normally enable the kidney to handle an increased solute load such as that produced by giving G 500, although for maximum effectiveness of the drug, Stamey (1972) recommends avoidance of diuresis. The solubilities of calcium phosphate and of magnesium ammonium phosphate depend both on the concentrations of the ions present and on the pH. Urines become increasingly supersaturated with respect to these salts as the pH rises from 6 to 7. In addition, G 500 increases the excretion of ammonium ions. In the presence of urea-splitting organisms it may be impossible to acidify the urine, and since the combination of alkalinity with increased outputs of calcium, magnesium, ammonium and phosphate favours stone formation, therapy with G 500 would appear to be contra-indicated when there is infection by urea-splitting organisms.

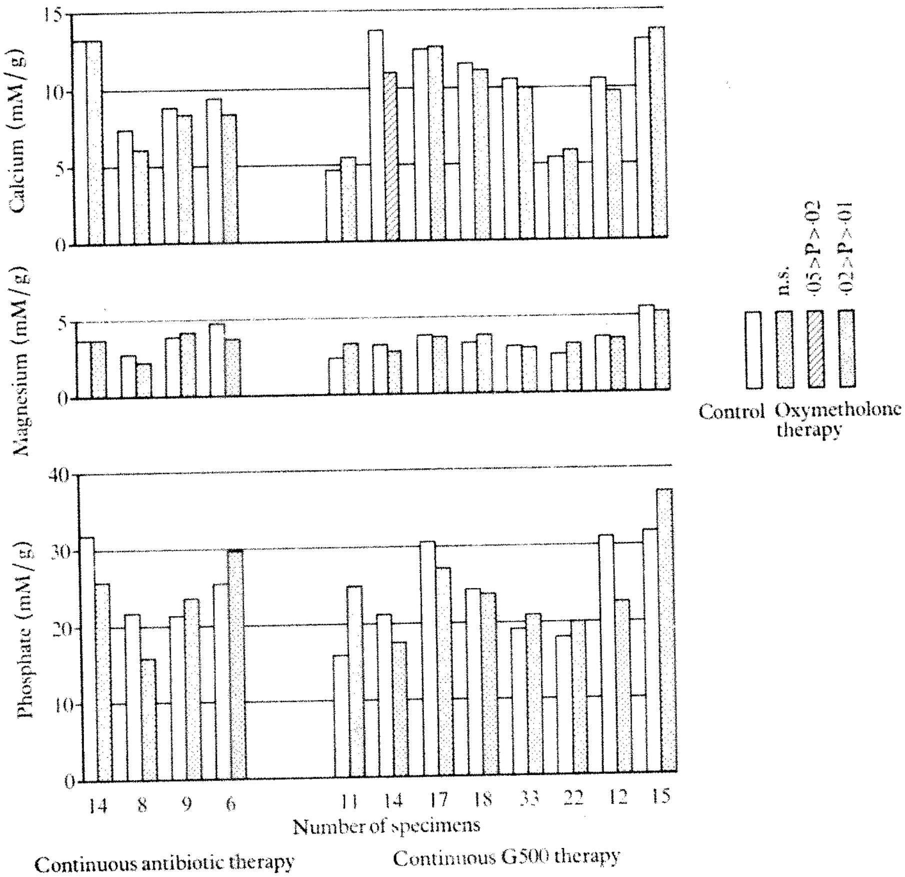

Fig. 3. Urinary excretion of calcium, magnesium and inorganic phosphate (expressed as ratios to creatinine excretion) in patients 6 weeks to 3 months after spinal cord injury. Oxymetholone given 10 mg at 6.00 hours daily for 4 weeks, stopped for 2 weeks, then cycle repeated. Three consecutive 24-hour urine collections obtained at middle and end of each 4-week period, and at end of each 2-week period. Means for control and test specimens are shown.

Summary

The effect of the simultaneous administration of hexamine mandelate and methionine on the urinary excretion of calcium, magnesium and phosphate is reported in 3 groups of paraplegic patients.

Long-term therapy with G 500 increases bone loss in paralysed patients, and is contra-indicated when there is infection of the urinary tract by urea-splitting organisms.

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The Urodynamic Assessment of Adult Enuresis

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The management of resistant adult enuresis continues to present considerable problems, despite recent encouraging results from bladder transection (Essenhigh and Yeates, 1973; Gibbon *et al.*, 1973). The various conservative and surgical therapies available tend to be employed empirically because of the lack of any satisfactory patho-physiological explanation for the disorder.

Childhood enuresis has been more extensively studied (Ellison Nash, 1949; Linderholm, 1966, Pompeius, 1971) and it is usually assumed that the childhood pattern of incompletely inhibited reflex bladder activity is prolonged into adult life. However, the variability in concurrent diurnal symptoms emphasises that the true neurophysiological basis of enuresis is more complicated than this, and involves potential abnormalities at several different neurological levels between the bladder and the cerebral cortex.

In an attempt to clarify these functional abnormalities, and to provide a more rational basis for treatment, an unselected group of adult enuretics have been studied objectively with a routine series of urodynamic investigations.

The definition of enuresis used is that of Ashton Miller (1966)—a normal reflex act of micturition occurring while the patient is asleep.

Patients and Methods

54 post-pubertal patients with enuresis were referred to the Clinical Investigation Unit of the Department of Urology at Ham Green Hospital, Bristol, between 1971 and 1973.

The programme of assessment was as follows: (1) Clinical features recorded on a standardised proforma for punch card analysis. (2) Unsupervised urinary flow rate. (3) Urethral pressure profile (Brown and Wickham, 1969). (4) Inflow cystometrogram (constant inflow 50 ml/min, temperature 37°C, constant recording via an epidural cannula per urethram). (5) Micturating cystometrogram (pressure/flow analysis).

Bladder and urethral pressures were measured after electronic subtraction of rectal pressure. All recordings were made on an 8-channel Elema Schoenander Mingograf following established techniques (von Garrelts, 1956; von Garrelts and Strandell, 1972). The urodynamic assessment was repeated 3 or more times in 17 patients, and the results were sufficiently comparable to assume that a single analysis was adequately representative.

Selected urodynamic results were also transferred to punch cards for analysis. The results were compared with "normal" recordings taken from a series of 15 age-matched patients with minor urological symptomatology who appeared to have no pathological abnormality on thorough investigation.

Intravenous pyelography, micturating cystourethrography and cystoscopy were performed on separate occasions.

Results

The 54 lifelong enuretics studied included 8 cases who had had a prolonged dry spell around puberty but had since relapsed. There were also 4 older males whose lifelong enuresis was converting to nocturia at about the age of 30 to 40 years, and who will not be considered further.

The distribution of these cases by age and sex is shown in Table I.

1. **Clinical Features.** Analysis of the severity and progression of symptoms gave much the same results in both sexes (Tables II and III).

Table I

Distribution of Enuretics Studied by Age and Sex

Age	10-19	20-29	30-39	40-49	50+
Male	9	17	4	2	0
Female	7	8	2	1	0

Table II

Frequency of enuresis	Males	Females
5 times per week	13	7
2-5 times per week	12	6
2 times per week	7	3

Table III

Progression of enuresis	Males	Females
Worsening	4	4
Static	19	10
Improving	9	2

A disproportionate number (5/8, 62%) of those who considered their symptoms were worsening came from the group where enuresis was a recurrent symptom following a dry period.

No neurological or psychiatric abnormalities were recorded among the males. Three of the females, however, suffered from idiopathic epilepsy; one of these had neurofibromatosis. The incidence of spina bifida occulta was 6% (3/48) no greater than in the normal population. There was one case of hypospadias and one of meatal stenosis. A positive family history of enuresis was obtained in 6/32 males (19%) and 5/15 females (33%).

The presence of diurnal symptoms has been regarded as a valuable indication of prognosis (Ashton Miller, 1966). In this series the majority of cases had some diurnal dysfunction. Frequency was present in 20/32 males (62%) and 10/15 females (66%). Urge incontinence occurred in 14/32 males (44%) and 10/15 females (66%). The relative infrequency of urge incontinence among males may be explained by differences in sphincter function (v.i.).

2. **Cystometric Assessment.** The cystometrogram was frequently abnormal. Uninhibited activity was common and occurred in 35/50 cases (70%) of whom 24/32 were male (75%) and 11/18 female (61%). These abnormal cystometrograms took three forms (Fig. 1).

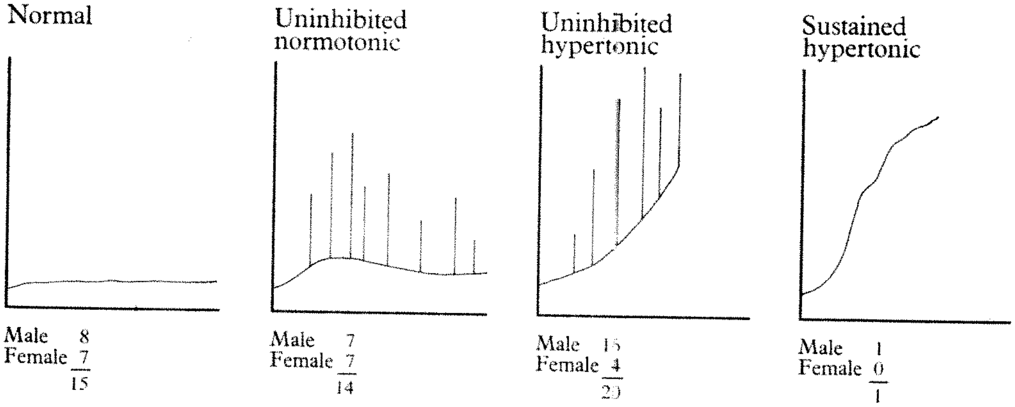

Fig. 1. Diagrammatic representation of the types of cystometrogram found in enuresis.

Table IV

Cystometrogram Capacity in Enuresis

	Mean capacity (ml) ± S.D.	
Enuretic subjects	Males	Females
Normal bladders	468 ± 121	456 ± 130
Uninhibited bladders	287 ± 106	362 ± 159
	$P < 0.001$	$P \neq$ not significant

Table V

Correlation between Symptoms and Uninhibited Contractions

	Uninhibited	Normal	Totals
Urge incontinence	18	6	24
No urge incontinence	14	8	22
Totals	32	14	46
Frequency	21	9	30
No frequency	11	5	16
Totals	32	14	46

The relatively large number of males in the uninhibited hypertonic group may also be explained by differences in sphincter function (v.i.). The lone male in the sustained hypertonic group had outflow tract obstruction.

Functional bladder capacity may be reduced in enuresis both by hypertonicity and uninhibited activity. The average cystometrogram capacity was 336 ml in males and 396 ml in females. An analysis of capacity *vs.* uninhibited activity is made in Table IV. The more significant difference in males is due to the higher proportion of hypertonic bladders.

Ellison Nash (1949) was able to correlate diurnal symptoms in enuretic children with the degree of uninhibited activity and with the prognosis. No similar association exists in the adult population tested here (Table V).

Use of the chi-square test shows no significant correlation between urge incontinence or frequency and the presence of uninhibited contractions (chi-square = 0·7 and 0·007 respectively). This may appear to be a puzzling situation and will be discussed below.

3. **Sphincterometry.** The urethral sphincter activity can be assessed in terms of the pressure it can produce or withstand. Using the urethral pressure profile technique, the activity can be measured in various parts of the urethra and peak values recorded for comparison at rest and on voluntary contraction. The length of time a contraction can be sustained can be measured. The pressure at which any involuntary leakage occurs (while the patient is attempting to remain continent) is an index of sphincter activity under these particular conditions.

The mean urethral sphincter pressure in normal and enuretic subjects is given in Table VI.

It is evident that there are no significant differences between normal subjects and enuretics analysed as a group. However, if the cases with hypertonic bladders are selected out, certain

Table VI

Urethral Sphincter Activity in Enuresis

	Mean urethral pressure (mm Hg) ± S.D.	
	Resting	Voluntary contraction
Normal male	78·1 ± 21·1	147·8 ± 24·8
Enuretic male	68·9 ± 22·2	154·6 ± 61·6
Normal female	66·5 ± 22·7	92·0 ± 24·7
Enuretic female	76·4 ± 28·8	103·7 ± 32·1

Table VII

Pressure/Flow Analysis in Enuresis

	Males		Females	
	Mean	Range	Mean	Range
Peak flow pressure (mm Hg) (P)	61·2	24-110	48·8	25-75
Peak flow rate (ml/sec) (F)	28·0	11-40	29·6	19-54
Outflow resistance (P/F^2)	0·113	0·04-0·48	0·086	0·009-0·175

discrepancies appear. In the hypertonic enuretic male the mean contracted sphincter pressure is 160·5 mm Hg ± 70·1 (P not significant). In the hypertonic female enuretic group both mean resting and mean contracted sphincter pressures are raised to 94·5 mm Hg ± 31·7 ($P<0·05$) and 127·0 mm Hg ± 18·9 ($P<0·005$) respectively. It would seem that, in the female enuretic, bladder hypertonicity results in some compensatory sphincter hypertrophy.

In a small number of cases (1 male, 3 female) involuntary leakage of urine occurred at a pressure less than the voluntary contraction pressure previously demonstrated. This introduces the concept of involuntary sphincter inhibition. Further support for this hypothesis was obtained from urethral pressure profiles performed during involuntary bladder contraction. The sphincter pressure was seen to fall reflexly, and could not be increased by voluntary sphincter contraction. Because of reciprocal innervation the concept of an overinhibited sphincter is just as valid as that of an uninhibited bladder. The two conditions may or may not exist together in any one patient.

4. **Micturating Pressure/Flow Analysis.** Enuresis has been associated with obstructive uropathy both in children (Mahony, 1971) and adults (Ashton Miller, 1966). Micturating pressure flow analysis is perhaps the best method for objective assessment of outflow tract function. The results of analysis in enuretic adults is shown in Table VII.

These values in general fall within normal limits for the age and sex of the patients concerned. If one accepts values of outflow resistance to be normal below 0·25 for males and 0·15 for females, then only 1/22 males and 2/13 females have some slight evidence of outflow tract obstruction. Cystoscopy, however, showed trabeculation in 23/31 cases (74%), with bladder neck hypertrophy in 12/22 males (54%) and 2/9 females (22%). 5/22 of the males (23%) also had a subvesical pouch, and in these cases the mean contracted sphincter pressure is significantly increased (200·2 mm Hg, $P<0.05$). Clearly there must be some explanation for these features other than the traditional outflow tract obstruction.

Discussion

The information presented above raises a number of questions which will be discussed in turn.

There appears to be a regression of the symptoms of enuresis with age, and indeed few patients are seen in the fourth decade and beyond. This impression may be true, or it may be due to the strong referral bias to the second and third decades. A review of the natural history of the various older patients seen by the unit confirms the impression of Yeates (1973) that there are 2 principal methods by which enuresis may regress. Firstly, there may be a true regression of both enuresis and diurnal symptoms; usually in these cases diurnal symptoms disappear first. Alternatively, the enuresis may convert to nocturia and the diurnal symptoms, including urge incontinence, may well remain. In this second group there is only an alteration of sleep pattern and the true pathological situation continues unabated.

Perhaps the most important question is why enuresis should occur at all if the bladder has a normal functional capacity and no uninhibited contractions? Equally, why should there be diurnal symptoms if there are no uninhibited contractions? There are three main levels of abnormality that may contribute to this situation. These are firstly disturbances of sensory function, secondly disturbances of cortical arousal or subconscious cortical inhibition and thirdly abnormal sphincter function.

Yeates (1972) introduced the concept of hypaesthetic urgency, where a sensory abnormality prevents the full appreciation of bladder distension or of an uninhibited contraction. This could theoretically prevent the maturation of normal inhibitory activity. Our analysis of this problem showed no differences in sensation between enuretic subjects and other patients who exhibit involuntary bladder contractions. The timing of the sensation of urgency was exactly at the onset of a detrusor contraction. An important point, however, is that this sensation of urgency was abolished in a small number of enuretic subjects by the use of urethral anaesthesia. In fact, urge incontinence became unconscious incontinence. This would suggest that there was some abnormality in the development of sensory receptors. It would seem that an inadequate trigonal sensation of tension was present, and the bladder contraction was appreciated by posterior urethral receptors only after the bladder neck had opened.

Clearly if sensation is normal the pathogenesis of enuresis must involve defects of cortical and subcortical activity during sleep. This could either take the form of inadequate cortical activation or the inadequate learning of conditioned reflexes. Either of these would prevent a normal subconscious inhibition of bladder activity from taking place. The information on cortical arousal during enuresis is very sparse. Ditman and Blinn (1955) have demonstrated that a pseudo-wakeful state occurs with marked α activity but that the subject remains unconscious. They attributed this to a psychological repression phenomenon. Pierce (1963) found three-fifths of his subjects were deeply asleep by E.E.G. criteria at the moment of enuresis. Whatever the situation, it is clear that sensation from the bladder does reach and alter cortical activity in some cases. The majority of subjects in our study confirmed that they slept abnormally deeply and were difficult to rouse.

The other abnormality that may be a contributory factor, in the absence of uninhibited bladder activity, is the over-inhibited sphincter mentioned earlier. Sphincter inhibition may occur reflexly as a result of bladder contraction, but it may also occur as an independent pathological entity. Apart from the evidence presented above, Franksson and Petersen (1955) noticed electromyographic sphincter abnormalities in two young male enuretics. They showed spontaneous sphincter relaxation on bladder filling. King (1971) also described 7 children who had a reversal of normal sphincter activity with paradoxical sphincter relaxation. The presence of inhibitory fibres to the

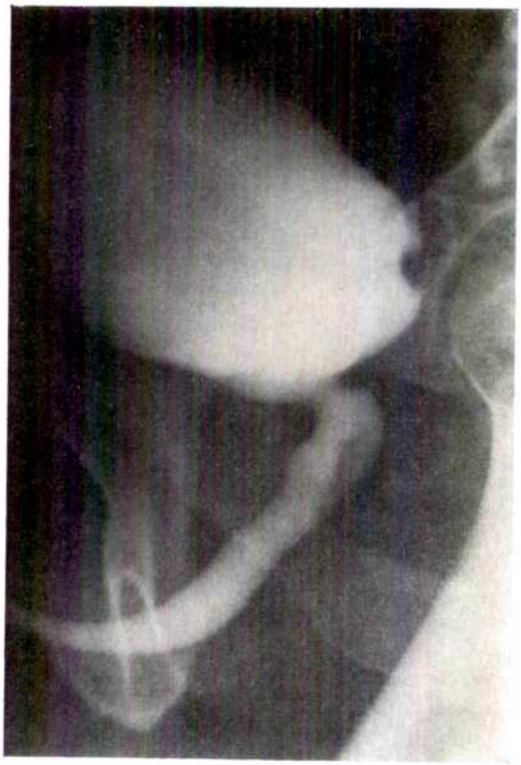

Fig. 2. The micturating cystourethrogram in a male lifelong enuretic showing bladder neck prominence that does not cause outflow tract obstruction.

urethral sphincter in the S4 nerve root has been suggested by other work from this unit (Torrens, 1974). These sphincter abnormalities in particular may explain the presence of urge incontinence in patients without uninhibited activity.

The other question that arises is why there should be trabeculation and bladder neck hypertrophy in the absence of outflow tract obstruction. The likely cause, as suggested by Gibbon (1966), is that there is neurological inco-ordination and hyperactivity of bladder muscle leading to work hypertrophy. However, if extra work is to be performed it must be against some form of resistance. As urinary pressure/flow relationships are normal this resistance is presumably the intermittent voluntary action of the external urethral sphincter (Yeates, 1973). This concept is confirmed by the observation of a statistically significant association between bladder hypertonicity and sphincter hypertrophy. It is undoubtedly true that transurethral resection of the bladder neck improves some cases of enuresis (Ashton Miller, 1966). As there is usually no obstruction to be relieved, the question arises as to how the improvement comes about. Perhaps the resection alters the balance of sensory activity in the trigonourethral area, or renders the posterior urethra in continuity with the bladder.

It is now possible to describe and explain some of the clinical features of the typical severe adult enuretic bladder. Intravenous pyelography is probably normal, although there may be a suggestion of trabeculation and a thickened bladder wall may be shown. Micturating cystourethrography (Fig. 2) and cystoscopy may show some trabeculation with hypertrophy of the interureteric bar and bladder neck prominence. Below the bladder neck the urethra is sometimes dilated. This is not a post-stenotic dilation but a pre-sphincteric ballooning. The fact that continence is frequently maintained by the hypertrophied urethral sphincter means that the bladder pressure is expended on the posterior urethra above the sphincter, causing it to become distended. The observation that males have a relatively decreased incidence of urge incontinence, an increased incidence of hypertonia on cystometrography and a more prominent subvesical pouch, presumably reflects the capacity of the male voluntary sphincter to contract and hypertrophy. It is our impression that involuntary sphincter inhibition is commoner in females.

Enuresis clearly remains a complicated and perplexing phenomenon. However, all levels of abnormality would seem to be mediated by the nervous system, and it is in the modification of nervous activity that a cure may be sought.

Summary

Urodynamic analysis has revealed a high proportion of uninhibited bladder activity in adult enuresis. There was no associated neurological deficit to explain this abnormality. There was no correlation between the various diurnal symptoms and the presence of uninhibited bladder contractions. Enuresis was associated with obstructive uropathy in only 6% of cases. Some evidence has also been presented to support the concepts of ectopic sensory receptors and abnormal sphincter inhibition.

A review of the problem of pathogenesis has suggested four main areas of possible abnormality:

1. A sensory lesion producing inadequate or delayed appreciation of bladder activity.
2. Cortical and subcortical dysfunction because of inadequate arousal or defective maturation of subconscious inhibition.
3. A congenital or acquired upper motor neurone lesion causing an uninhibited bladder.
4. A similar or related lesion causing an over-inhibited sphincter.

These factors probably always occur in varying combinations. Because of the lack of association between symptoms, signs and objective measurements, there is a strong case for relating diagnosis, prognosis and treatment to urodynamic assessment.

We wish to thank the many surgeons in the South West Region who referred their patients for investigation.

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Radiation Enteritis following Radiotherapy for Prostatic Carcinoma

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Orthovoltage radiotherapy was first used for the treatment of prostatic carcinoma during the 1920s. Early enthusiasm was soon tempered by the limited therapeutic results obtained and the frequent occurrence of severe complications. The limited results were interpreted to mean that prostatic carcinoma, like other adenocarcinomas, was relatively radio-resistant. In 1941 the discovery that prostatic carcinoma was responsive to hormonal treatment caused diminished interest in radiation therapy. The encouraging report of Bagshaw, Kaplan and Sagerman in 1965, using supervoltage sources and new techniques of application, generated renewed interest in radiation therapy and today there is considerable support for the use of supervoltage therapy for treatment of locally invasive prostatic carcinoma. Supervoltage therapy is reported to yield good therapeutic results accompanied by fewer and less significant complications than low energy sources. Little attention has been given in recent years to the complications of radiation therapy. Herein are reported 2 cases of radiation enteritis and small-bowel obstruction following supervoltage radiation therapy for carcinoma of the prostate. The 2 cases were unique in our series in that both underwent laparotomy shortly prior to beginning radiation therapy. The purpose of this paper is to review briefly the present status of radiation therapy for carcinoma of the prostate and to discuss certain significant and possibly avoidable complications.

Case Reports

17 patients have been treated for carcinoma of the prostate with cobalt radiotherapy at our institution over a 2-year period. 13 patients had Stage C or locally invasive disease. There were 2 Stage D patients treated primarily for relief of ureteral obstruction. 2 Stage B patients were treated; 1 refused radical prostatectomy and 1 was considered unsuitable for operation by reason of age.

The diagnosis of prostatic carcinoma was established by needle biopsy or transurethral resection of the prostate. All patients were staged by rectal examination, skeletal survey, serum acid phosphatase determination and strontium-85 bone scan. In addition, 2 patients underwent transperitoneal exploration and hypogastric lymph node biopsy.

Case 1: G. S. (No. 017063). A 49-year-old white man was admitted following his second episode of urinary retention. On physical examination the prostate was hard and irregular with superior and lateral pelvic extension. The intravenous urogram revealed normal upper urinary tracts. Serum acid phosphatase was elevated by 4 separate determinations although the skeletal survey and strontium-85 bone scan was negative. A transrectal needle biopsy confirmed the diagnosis of moderately differentiated carcinoma. A transurethral resection of the prostate was performed. Transperitoneal hypogastric lymph node biopsy was done to determine accurately the local extent of tumour and positive nodes were obtained bilaterally. The patient received 6,000 rads of external cobalt radiation to the prostate and pelvis to the level of the iliac bifurcation over 5 weeks along with 1 mg of diethylstilboestrol daily. During radiation therapy he experienced mild symptoms of rectal tenesmus and tenderness which subsided after treatment. Six months later he presented with crampy abdominal pain and distension. Abdominal films confirmed the clinical diagnosis of small-bowel obstruction. The patient failed to respond to conservative therapy including long-tube suction. Laparotomy revealed the terminal small bowel to be markedly oedematous and involved in massive pelvic adhesions requiring bowel resection. Histologic examination revealed loss of epithelial cells and lymphoid tissue as well as marked oedema and proliferation of fibrous tissue in the submucosal layer. These findings were felt to represent radiation enteritis.

Case 2: W. K. (No. 028483). A 57-year-old man was referred for evaluation of a prostatic nodule and a palpable right flank mass. An intravenous urogram showed a normal somewhat enlarged left kidney. The right kidney appeared to have a small functioning upper portion accompanied by a large lower pole mass. Renal arteriography revealed the mass to be avascular and probably cystic. Needle biopsy of the prostatic nodule confirmed the diagnosis of prostatic carcinoma. Acid phosphatase determinations and a strontium-85 bone scan were normal. Laparotomy revealed a hydronephrotic right lower renal segment and a right nephrectomy was performed as well as hypogastric lymph node biopsy. The nodes were negative for tumour. The patient refused radical prostatectomy and was treated with 6,000 rads of external cobalt therapy over a 5-week period. During therapy he experienced rectal pain and diarrhoea. Four months later he presented with small-bowel obstruction which failed to improve with conservative therapy. Laparotomy revealed extensive small-bowel adhesions requiring resection. The resected bowel showed changes consistent with severe radiation enteritis.

Discussion

Definitive treatment for localised intracapsular carcinoma of the prostate was established by Young in 1905 with the development of the radical perineal prostatectomy. Unfortunately, there is no effective therapy for cure of extracapsular carcinoma of the prostate, whether locally invasive or metastatic. Soon after the development of radiation therapy it was proposed that this technique might provide curative therapy for regional disease. There were early reports of treatment of both locally invasive and metastatic disease with radiation therapy (Bumpus, 1922; Deming, 1922; Smith and Peirson, 1930). The therapeutic results were mainly limited to relief of pain and obstructive symptoms although there was a rare report of apparent tumour cure. Prolongation of survival over that of untreated controls was also reported (Bumpus, 1922). In 1932 Widman reported prolonged survival and marked relief of both painful and obstructive symptoms in a group of irradiated patients and optimistically stated that the disease was quite amenable to radiotherapy. By 1942 Barringer, based on his 15-year experience at Memorial Hospital, stated that deep X-ray therapy had been of little help in controlling carcinoma of the prostate. In 352 cases he reported a 5-year survival of 10% and a 10-year survival of 6%. These figures were essentially the same as those reported prior to the use of radiation therapy. The common complications reported at this time included nausea, weakness, skin necrosis, rectal ulcers, urethral strictures and recto-urethral fistulae.

It was at this time that Huggins and Hodges (1941) reported their work on endocrine therapy for extracapsular prostatic carcinoma. Orchidectomy and oestrogens rapidly became established as an excellent palliative mode of therapy for this disease. Such was the acceptance of endocrine manipulation, that figures from the California Tumour Registry for the 15-year period 1942 to 1956 showed that of 2,500 cases of carcinoma of the prostate gland only 5 received local radiation therapy. Following the report by Flocks *et al.* (1952) that radioactive gold inserted or injected directly into the prostate could result in tumour shrinkage, radiotherapists and urologists reconsidered the use of radiation therapy as a curative technique. External radiation using modern supervoltage techniques was evaluated by several groups (Bagshaw, Kaplan and Sagerman, 1965; George *et al.*, 1965; Del Regato, 1967). Their results indicated that a significantly increased 5-year survival could be expected over that being reported wirh hormonal methods. Negative biopsies were obtained as long as 8 years after completion of therapy (George *et al.*, 1965; Bagshaw, 1969). These authors agreed that patients with Stage A or B lesions should be offered a radical prostatectomy but treatment with radiation recommended if they refuse operation or were considered medically unfit for surgery. It was also agreed that Stage D patients should be excluded unless being treated for metastatic symptoms.

Several large series of patients with longer follow-up periods have been reported (Bagshaw, 1969; Grout *et al.*, 1971; Carlton *et al.*, 1972). The results have been inconclusive with regard to cure but most agree there has been good relief of symptoms and local regression of disease as judged by rectal examination. Definite changes in tumour size and consistency may not be noted until several months following completion of therapy. Carlton *et al.* (1972) feel that post-treatment biopsies should not be done prior to 6 months but that a biopsy should be done after 12 months even if the prostate is palpably normal. He found tumour in 5 of 12 palpably normal glands 12 or more months post-therapy. Rhamy, Wilson and Caldwell (1972) reported residual tumour in 13 of 15 patients at time intervals ranging from 4 to 38 months post-treatment. They did not describe the findings on rectal examination at the time of the biopsies.

The complications reported during the course of external radiation therapy are generally of a minor variety and subside spontaneously (Bagshaw *et al.*, 1965; Dykhuizen *et al.*, 1968; Graham and Villaba, 1963). These include diarrhoea, dysuria, rectal bleeding, rectal ulcers, proctitis, rectal pain, erythema and epilation of the skin (George *et al.*, 1965; Bagshaw *et al.*, 1965; Del Regato, 1967; Grout *et al.*, 1971). Late complications are rarely reported. Bagshaw (1969) reports less than a 2% incidence of urethral stricture or urinary incontinence while Grout *et al.* (1971) report 1 case of 40 with urinary stress incontinence and 4 cases of 40 of stress fecal incontinence. Bagshaw (1969) claims impotence is difficult to evaluate but estimates that 75% retain potency. Grout *et al.* (1971) report only 2 cases of impotence. More disturbing is the report of Rhamy *et al.* (1972) in which 47% of their patients became impotent. Radiation therapy is often compared favourably to radical prostatectomy in terms of complications. Following radical perineal prostatectomy, virtually all patients are impotent and, with the exception of Jewett's series, urinary incontinence and severe urethral strictures occur in roughly 50% (Jewett, 1969; Young and Bohne, 1972). In several series there were no reports of severe small-bowel injuries following radiation therapy for prostatic carcinoma. It has been previously recognised in the gynaecological, radiological and surgical literature that the large and small bowel are quite susceptible to radiation injury (Graham and Villaba, 1963; Kaplan, Hudgins and Wall, 1965; Perkins and Spjut, 1962; Heffernon and Memik, 1969). These reports suggest that pelvic inflammatory disease and lymphadenectomy increase the incidence of radiation injury to the small bowel (Dodge, 1969; Strockbine, Hancock and Fletcher, 1969). DeCosse *et al.* (1969) found a positive correlation between the incidence of radiation injury to the gut during cancer therapy and the following factors: hypertension, arteriosclerosis and/or diabetes, and previous supracervical hysterectomy. There is evidence that arteriosclerotic and diabetic cardiovascular disease also increase the incidence of delayed radiation injury. It seems that any factor which produces bowel-wall ischaemia increases the possibility of significant radiation injury. In addition, any procedure which produces adhesions and fixes the small bowel in the pelvis increases the probability of small bowel radiation injury. A likely explanation in this latter circumstance is that these fixed loops of small bowel are unable to move out of the daily radiation field and receive a higher dose.

The initial radiation injury to small bowel is reversible and includes the loss of specialised epithelium and lymphoid tissue. In addition, the submucosal layer is involved by proliferation of fibrous tissue and a progressive obliterative vasculitis involves the intestinal vasculature (Dodge, 1969). It is ischaemia and fibrosis resulting from these permanent vascular changes, sometimes augmented by arteriosclerotic disease or diabetes, that produces the ulcers, strictures, and necrosis months or years later (DeCosse *et al.*, 1969). Partial or complete small-bowel obstruction may result, as occurred in our cases (DeCosse *et al.*, 1969; Heffernon and Memik, 1969).

Surgical assessment of the hypogastric lymph nodes may be a necessary and valuable step in the staging of selected patients. It is suggested that lymph node biopsy, if indicated, be done using an extraperitoneal approach.

Summary

Two cases of radiation enteritis and small bowel obstruction are reported following supervoltage radiation therapy for carcinoma of the prostate.

The mechanisms of radiation injury to the small bowel and contributing factors are discussed.

It is suggested that lymph node staging procedures for carcinoma of the prostate be done extraperitoneally in order to avoid the enhanced sensitivity of small bowel to radiation injury following transperitoneal procedures.

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In-vivo Determination of Error in the Measurement of Urethral Pressure by the Method of Brown and Wickham

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The method of urethral pressure profile measurement described by Brown and Wickham (1969) has been used in a number of studies over the past few years. Several of these have been reported in the pages of this journal. However, alternative methods of urethral pressure recording such as using catheter-tip balloons and force gauges are still used, even in situations where they are less suitable than the new method.

Reasons for not using the new method may be doubts about its accuracy or the assumptions which were made in the original paper. There can be no doubt that the principle of operation is not well understood by many people who have used it. This manifests itself in inaccurate results caused by inattention to system compliance, drip rate, withdrawal rate and use of inappropriate catheters and manometers.

The object of this short paper is to demonstrate that even if clinical results are confusing, the basic accuracy of the measuring technique is not at fault.

The Original Method

In the original method, water was infused into the urethra via side holes in a special catheter.[1] The pressure of the water in the catheter was claimed to approximate to the urethral wall pressure.

The difference between the measured pressure (that in the catheter) and the closure pressure of the urethral wall was estimated by varying the water infusion rate and recording the measured pressure. Extrapolation to zero infusion rate indicated the urethral wall pressure. These tests showed that the infusion rate affected the recorded pressure by about 2 cm H_2O for every ml/min of infusion rate. However, with the original apparatus it was not possible to estimate the flow accurately, nor change the rate without disturbance.

Determination of Pressure Error

A basic assumption about the technique is that the epithelium of the urethra would seal the eye of a urethral catheter to a pressure equal to the closure pressure of the urethra at the level of the eye of the catheter.

The fact that the urethral wall can contain a pressurised fluid in a catheter has been demonstrated by Lapides (Lapides *et al.*, 1960). A water column was allowed to discharge through a side-opening catheter in the urethra. Initially the water flowed quickly because of the large excess pressure, but as the pressure head of the column approached the urethral wall pressure, it slowed and finally stopped.

A method of error determination has been devised which uses an apparatus similar to that used by Lapides. A water column is allowed to discharge into a urethral pressure profile catheter[1]

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[1] Urethral pressure profile catheter, Endoscopic Instrument Company Limited, 62 Shirland Road, London, W.9.

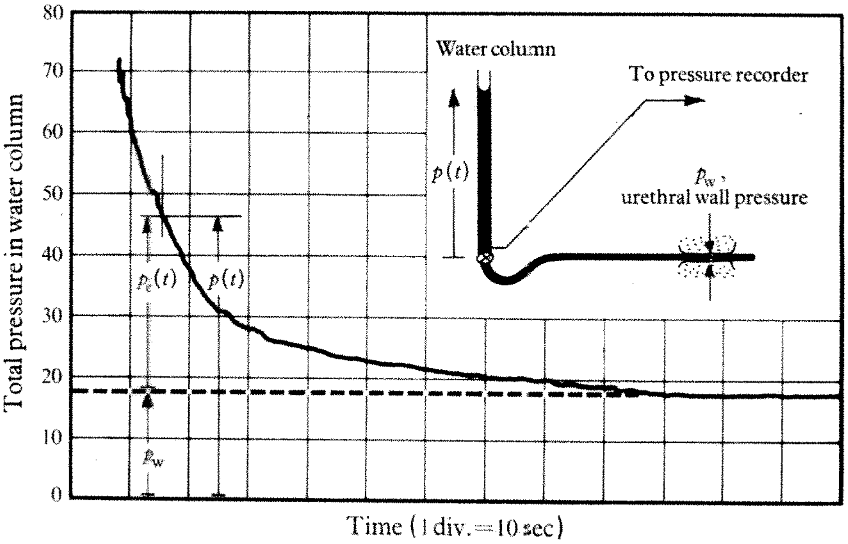

Fig. 1. Pressure decay occurring as a water column discharges into a female urethra through a size 12F urethral pressure profile catheter. The excess, or error pressure $P_e(t)$ is the total pressure $P(t)$ minus the urethral wall pressure P_w.

opening into the urethra. The pressure within the catheter (which corresponds to the head of water in the column) is recorded electrically. The record therefore shows pressures corresponding to a wide range of flow rates. The pressure at which flow stops is the actual urethral wall pressure. Figure 1 was traced from a test on a female urethra using a size 12F catheter.

As expected, the pressure shows a near exponential decay towards the urethral wall pressure, and by well-known analysis we can describe the curve by the expression:

$$P_e(t) = P_e(0)\exp\left(\frac{-t}{CR}\right) \tag{1}$$

in which P_e is the excess of pressure in the column over the eventual resting pressure, i.e. $P_e = P - P_w$.

t = time in seconds,
$P_e(0)$ = P_e at time $t = 0$,
$P_e(t)$ = P_e at time t,
C = volume compliance of the water column in millilitres of water stored per cm H_2O rise in pressure,
R = resistance to flow of water through the tubes, the eye of the catheter, and the urethra.

The resistance to flow is numerically the change in recorded pressure due to the flow itself, and represents the error caused by infusion.

Resistance can be extracted from equation (1) by taking logarithms:

$$\log\left[\frac{P_e(0)}{P_e(t)}\right] = \frac{t}{CR} \tag{2}$$

and re-arranging,

$$R = t/[\log P_e(0) - \log P_e(t)]C \frac{\text{cm } H_2O}{\text{ml/min}}. \tag{3}$$

Compliance C is numerically the cross-sectional area of the water column. A value for t can be found from Figure 2 by drawing a tangent to the curve. This will intercept the axes ($t = 0$ and $P_e(t) = 1$) to give corresponding values of $P_e(0)$ and t. Resistance can be calculated by substitution in equation (3).

Since errors below 1 cm H_2O would not be significant and those above 10 cm H_2O unacceptable, a mean value of resistance may be determined for this range. If $P_e(t)$ and $P_e(0)$ are 1 and 10 cm H_2O respectively, the equivalent value of t for this range is found from the time axis.

The mean resistance over this range was found to be 1·23 cm H_2O per ml/min of flow rate. A typical flow rate used during urethral pressure profile recordings is 2 ml/min, which would yield readings 2·46 cm higher than actual.

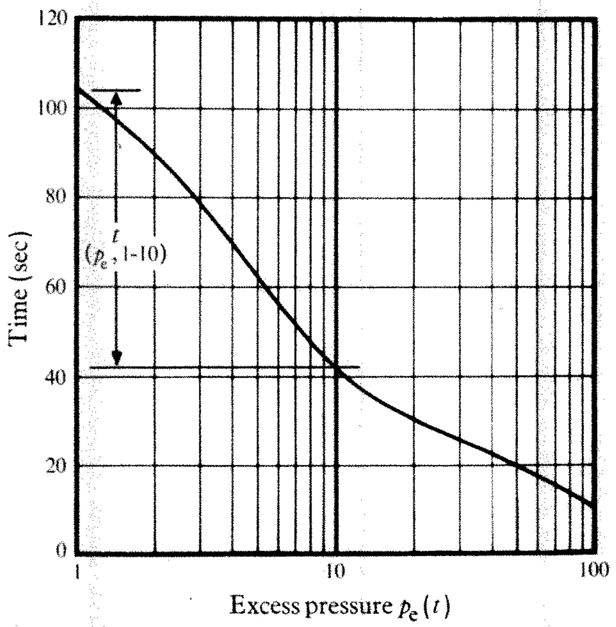

Fig. 2. Logarithmic plot of $P_e(t)$, the excess pressure in the water column over the urethral wall pressure. Resistance to outflow of fluid is characterised by the steepness of the curve. Notice that resistance is low at high values of excess pressure.

Some of this error occurs within the apparatus itself, and some is the "intrinsic error" of the method, occurring at the point of measurement and in the urethra. The error occurring within the apparatus was determined by repeating the test with the catheter withdrawn from the urethra. When this error is subtracted from the overall figure given above, the "intrinsic error" of the method is found to be 1·04 cm H_2O per ml/min—a very small figure.

Figure 1 shows an interesting effect. The last 2 or 3 centimetres of head drop are characterised by small steps in pressure. These are quite small on the paper recording but quite clear on the water column. This suggests that there are pressure fluctuations occurring within the urethra, and small quantities of fluid are released during the dips in pressure. These fluctuations are of the same order as the accuracy of the method.

Figure 2 shows that the resistance to flow is not in fact constant. It is interesting to note that resistance reduces at high flow rates. This is because the urethra dilates in response to the excess pressure—the same effect that occurs during micturition when the bladder provides the excess pressure.

Discussion

These results show that urethral pressure recorded by the method of Brown and Wickham will not be greatly affected by variations in flow rate. Errors are always positive and will therefore not appear in comparisons between results.

In recording complete profiles, other factors need observing. Typical failings are small leaks, air bubbles, excessive length of soft tubing in the pressure circuit, inadequate pressure head in the main reservoir, too slow a recording response time, and too high a withdrawal rate. Any of these can make nonsense of the results.

Edwards and Malvern (1974) make reference to a number of possible sources of error, of which "alterations in perfusion rate" appears to be the most serious. However, the profile used to demonstrate the effect exposes a slow response time, probably due to excessive lengths of soft tubing in the pressure circuit, or a high compliance infusion pump. In that particular case it would be wiser to improve the response time rather than increase the infusion rate. After allowing for the response time error, their result confirms the finding of this paper—that recorded pressure is little affected by infusion rate.

No attempt has been made here to indicate the value of the technique as a diagnostic aid. This is covered elsewhere, by Glen and Rowan (1973) and Edwards and Malvern (1974) for instance. The method clearly has some uses but most results so far have been interesting physiological data rather than help for the clinician. These failings are, however, more in the nature of urethral pressure than in the accuracy of urethral pressure measurements.

Summary

A method of determining the error caused by the infusion of water into the urethra during urethral wall pressure and urethral pressure profile measurements is described and discussed. The test is conducted *in vivo* and the measured pressure is related to the actual urethral wall pressure. The "intrinsic error" is found to be approximately 1·0 cm H_2O for every ml/min of infusion rate.

Incidental findings concerned with changes in urethral resistance are also reported.

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Hydrocolpos

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Hydrocolpos is a congenital lesion causing a fluid distension of the vagina, resulting from excessive genital secretion in association with vaginal obstruction. It is a condition of great rarity, and the method of presentation can produce alarming genito-urinary and abdominal signs, and as a result it is frequently misdiagnosed because the obstructive vaginal element is not always apparent even on routine examination. The method of presentation is variable, usually a lower abdominal mass associated with urinary symptoms either of frequency of micturition or complete retention. The fact that the condition is frequently encountered, and also incorrectly diagnosed may result in injudicious treatment often associated with a considerable morbidity and even mortality.

Three cases of hydrocolpos have been treated in the Department of Urology in the Royal Infirmary, Cardiff, in the last 10 years. The case histories and method of presentation are described.

Case Reports

Case 1. A 48-hour-old neonate was admitted to hospital because she had not passed urine since birth. The gestation and delivery were both normal. She was a healthy baby girl presenting with lower abdominal distension due to a smooth suprapubic mass arising from the pelvis which was dull to percussion. Examination of the vagina revealed a bulging membrane at the vaginal orifice, but neither the introitus nor the urethral opening could be visualised (Fig. 1).

Under general anaesthesia milky white fluid was aspirated from the distended vagina, following which the urethral orifice became evident in its normal position. The passage of a catheter enabled a large volume of urine to be drained and the suprapubic mass disappeared. The obstructing vaginal membrane was incised and further milky white fluid was released. Following withdrawal of the catheter 2 days later, urine was passed freely and no further collection of vaginal fluid was detected. On discharge from hospital she was well and asymptomatic and has remained so ever since.

Case 2. A 3½-week-old girl developed a right sided proptosis which rapidly resolved without treatment. However, during routine examination it was noticed that she was incontinent, the urine which was passed was purulent, and it was uncertain whether it was being discharged from the urethra or the vagina. The child on admission to hospital was ill and febrile, and a smooth dull mass was noted suprapubically. The urine contained excessive pus cells due to a B. Proteus and B. Coli infection. An intravenous pyelogram showed bilateral hydro-ureter and hydronephrosis with prominent lateral posterior displacement of both ureters.

Routine examination under anaesthesia spontaneously released a large quantity of milky fluid from the vagina and the abdominal mass disappeared. A diagnosis of hydrocolpos was made and in the absence of any demonstrable vaginal obstruction it was felt that the hydrocolpos had drained satisfactorily, and further surgical intervention was not performed at this stage. However, at the age of 1 year she still had a coliform urinary infection and was not thriving satisfactorily, and a low palpable abdominal mass was present. Laparotomy was performed and a grossly enlarged uterus was discovered, palpation of which caused further foul-smelling white fluid to drain from the vagina. The abdominal mass disappeared and the wound was closed. Unfortunately a complete examination of the vagina was not made at this time, and at a subsequent examination under anaesthesia it was noted there was still an antero-posterior septum across the vagina which had caused hydrocolpos. Division of the septum presented no difficulty and the cervix was then identified. There was, however, still evidence of retention of fluid in the uterus.

Convalescence was completely satisfactory, her general condition improved though subsequently bilateral re-implantation of the ureters for total vesico-ureteric reflux was required.

Case 3. A child of 6 months was admitted to hospital with anorexia, and vomiting of 2 days duration associated with generalised malaise. Examination revealed she was normally developed for her age, but was obviously ill and dehydrated. There was marked tachycardia and pyrexia. The blood urea was elevated, and there was a marked leucocytosis. A large lower abdominal mass was palpable extending above the umbilicus but did not appear to be arising from the pelvis. No abnormality was noticed on routine examination of the perineum or anal area. A urethral catheter passed easily into the bladder and 800 ml of blood-stained urine was drained, but in spite of this there was no appreciable diminution in the size of the abdominal mass.

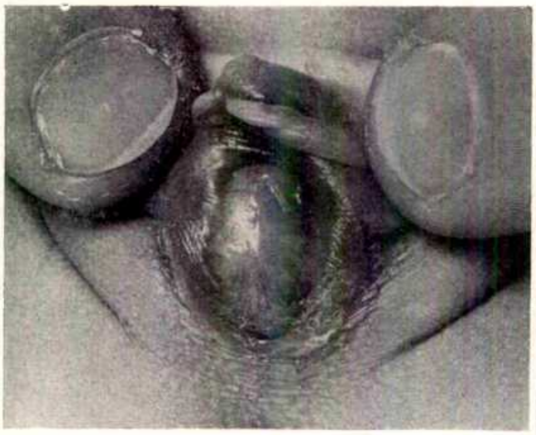


Fig. 1. Bulging vaginal membrane. Urethral orifice not visualised.

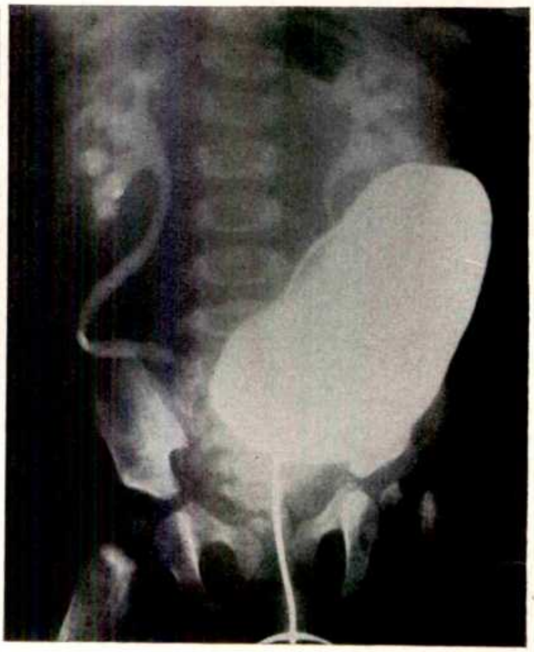


Fig. 2. Intravenous pyelogram combined with a cystogram. Vesical displacement together with upper urinary tract dilatation.

A pyelogram combined with a cystogram (Fig. 2) showed bilateral hydro-ureter and hydronephrosis, again with displacement of the lower end of the ureters laterally and posteriorly. The bladder was pushed forwards, upwards and to the left, and was grossly distended. Following resuscitation with parenteral fluids and antibiotics it was decided to perform a laparotomy to ascertain the cause of the vesical displacement and the ureteric obstruction; it was felt this was possibly a case of hydrocolpos even though the vagina appeared to be normal.

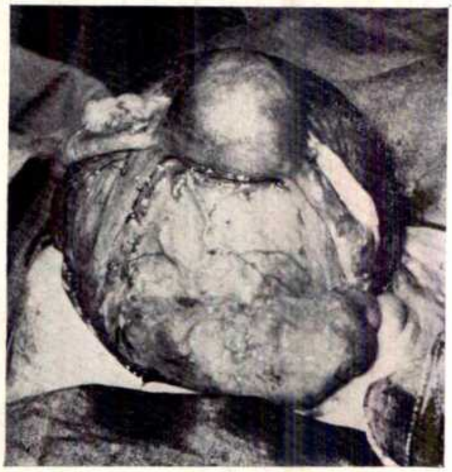
Laparotomy was performed through a lower right paramedian incision, and a large cystic mass was seen arising from the pelvis which consisted of a grossly distended vagina with the uterus, Fallopian tubes on the superior surface of the mass, and the bladder was attached to the anterior surface of the mass (Figs. 3 and 4). Aspiration of the cystic mass produced a large volume of milky white fluid, and incision of the vaginal fornix revealed a transverse septum in the vagina which was responsible for the large hydrocolpos. This was completely excised and the vagina drained by an indwelling tube. Postoperatively the convalescence was uneventful, micturition returned to normal, and the urethra was then seen to open in the more normal position.

Discussion

The term hydrocolpos implies a cystic dilatation of the vagina caused by retained cervical and vaginal secretion prior to puberty in association with vaginal obstruction. The term hydrometrocolpos is used when the uterine cavity is also distended with fluid (Case 2). Perhaps the more common presentation of vaginal obstruction occurs after puberty, and is usually due to retained menses, the condition of haematocolpos.

Vaginal obstruction causes hydrocolpos only when there is associated excessive genital secretions mainly of cervical origin, due to maternal hormonal stimulation of the cervical mucous glands. Obstruction may result from an occluding membrane across the vagina either as a true imperforate hymen, or alternatively as a narrow atretic segment due to failure of vaginal development. Doubt exists as to the development of the vagina; Koff (1933) described a Mullerian component which formed the upper 4/5ths of the vagina which fused with a lower component derived from the urogenital sinus. It was postulated that the transverse septum was due to failure of fusion of these two components, a theory not acceptable to Deppisch (1972).

It is now considered that cases of vaginal atresia result from an embryonic arrest in vaginal development, resulting in failure of canalisation of the solid cellular structure which is later to form the true vagina. The degree of atresia is proportionate to the extent of vaginal canalisation.



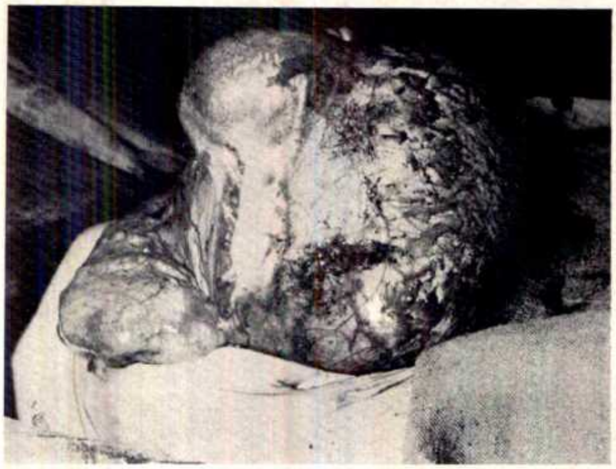


Fig. 3. Anterior view of mass at laparotomy.

Fig. 4. Lateral view of mass at laparotomy. Bladder is anterior to the mass.

Therefore, two conditions must be operative to produce hydrocolpos. Primarily, obstruction of some part of the vagina is necessary and, secondly, excessive secretion from the genital glands, chiefly the cervical group, as a result of hormonal stimulation. This excessive secretion can occur in the neonatal and prepubertal periods, but is found to be more common in the neonate (Spencer and Levy, 1962).

Godefroy reported the first authentic case of hydrocolpos in 1856 and since then further cases have appeared in the literature. Reviewing the literature from 1900, Cook and Marshall (1964) reported 77 cases of hydrocolpos, and 58 of these had occurred since 1940. In this group of 58 cases, 49 occurred in infants less than 10 months old, in fact, 33 within the first week.

The clinical picture varies greatly and can cause diagnostic confusion and inaccuracy. Most commonly an abdominal mass, or lower abdominal distension, is present and in many cases this is caused purely by the hydrocolpos, but on occasions there is associated urinary or bowel obstruction which augments the size of the abdominal mass (Spencer and Levy, 1964). The mass may be large enough to cause respiratory embarrassment and is often associated with lower limb oedema which is an indication of pelvic venous obstruction. Obstruction to the bowel commonly presents as abdominal distension associated with constipation and spurious diarrhoea, the result of compression of the lower bowel by the hydrocolpos mass. Urinary retention with vesical distension may be the only evidence of involvement of the urinary tract, but on occasions, as a result of subacute urinary retention, infection is frequent. Not uncommonly, hydronephrosis, hydro-ureter, pyelonephritis and chronic upper urinary tract damage may result (Cook and Marshall, 1964; Brinton, Lynn and Logan, 1970).

Urinary obstruction may occur on its own, but in a review of 62 cases by Spencer and Levy it was noted that often intestinal and venous obstruction were associated with urinary tract obstruction. The abdominal mass is characteristically smooth, rising out of the pelvis, and though often large and central it may be eccentric in position. Catheterisation of the bladder may cause some reduction in the size of the mass due to emptying of the bladder but obviously has no effect on the associated hydrocolpos. In some cases where a bulging membrane is clearly seen at the vaginal orifice it is often impossible to identify the urethra, which becomes displaced superiorly and lies posterior to the symphysis pubis. In certain cases the obstructing septum may be drawn up from the perineum, especially when a large hydrocolpos has to occupy the abdominal cavity rather than the restricted confines of the bony pelvis. Though the perineum may at first appear normal, careful examination should reveal the true state of affairs, and in all cases a definite attempt must be made to identify the cervix. This is a most important physical sign in diagnosing hydrocolpos.

Pyelography and cystography show characteristic lateral displacement of the ureters and forward and lateral displacement of the bladder (Figs. 3 and 4).

Laparotomy is frequently performed as a result of failure to make the correct diagnosis and in a series of 49 cases, reported by Gravier (1969) between 1940 and 1964, this method of treatment was performed in 24 cases. In this series there was a 50% mortality following operative intervention, and of the remaining 26 cases 5 died. Spencer and Levy reviewed 44 infantile cases and noted a proportion of these deaths was due to associated multiple congenital anomalies as a result of laparotomy, and in the remaining 3 the result of inadequate treatment. When there is a bulging membrane at the vaginal orifice, aspiration of milky white fluid from the cystic vaginal cavity makes the diagnosis obvious, and treatment usually requires a simple linear or cruciate incision through the obstructing membrane. The retained fluid drains rapidly, but it is advantageous to drain the vagina by an indwelling tube for a short time, and on occasions a more complete excision of the obstructing membrane may be required.

When the obstruction is due to high vaginal atresia a combined abdominal and perineal approach is utilised in order to produce adequate drainage of the hydrocolpos. The abdominal incision into the dilated vagina is similar to that used in a low Caesarian section, and this not only allows drainage of retained fluid, but permits inspection of the upper portion of the vagina so that the obstructing transverse membrane may be incised from above. Again, tube drainage of the vagina is usually employed in the postoperative period for a period of 48 hours. In a review of 58 cases by Cook and Marshall only 50% had been correctly diagnosed before treatment was instituted. The overall mortality rate in this series was 35%, and of those subjected to laparotomy 50 died. They stressed that the most important single adjunct to a correct diagnosis was adequate vaginal examination to identify the cervix uteri. These results are truly disappointing and depressing and testify to the severity of the condition in the newborn if an incorrect diagnosis is made combined with inadequate treatment.

Summary

The method of presentation and problems in diagnosis of 3 cases of hydrocolpos are discussed.

The anatomy and embryology of the abnormality is described.

The methods of treatment and results are outlined.

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The Microbial Flora of the Vagina and its Relationship to Bacteriuria in Diabetic and Non-Diabetic Women

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Various studies have shown that symptoms such as urinary frequency, dysuria, pruritus vulvae and the presence of vaginal discharge do not necessarily correlate with significant bacteriological findings in the urinary or vaginal flora (Gallagher, Montgomerie and North 1965, Hunter and Long, 1967). There is no general agreement as to what constitutes a "normal" vaginal flora, since the bacterial population may be influenced by such diverse factors as age, pregnancy and the stage of the menstrual cycle. However, it has been suggested that, in some cases, bacteria resident in the genital tract may become the cause of urinary tract infection. (Stamey *et al.*, 1971).

The aim of this study was to examine the microbial flora of the vagina, and to relate the findings to urogenital symptoms, menstrual status and concurrent bacteriuria. Since it is commonly believed that genito-urinary infection is commoner in diabetics, the relationship of the findings to the presence or absence of diabetes was also studied.

Patients and Methods

90 patients (57 diabetic and 33 non-diabetic) were studied. These 2 populations were assessed in terms of age, parity, hospital in- or out-patient status, sexual activity and the presence of urogenital symptoms; in all these respects they were statistically comparable. The mean age of the groups was 57 and 50 years respectively. 42 patients had established diabetes; in these women, an arbitrary assessment of control over the preceding year was made and graded "good", "moderate" or "poor". In the remaining 15 diabetic women, the condition was of recent onset. Patients were examined either in the out-patient clinic or in a general medical ward. Those patients who were acutely ill, had undergone a gynaecological operation, had been catheterised, or had received antibacterial therapy during the preceding month, were excluded from the study. Women who had had intercourse within two weeks of examination were regarded as being sexually active.

Serum-coated cotton wool swabs were inserted through a sterile unlubricated speculum, to obtain material from the posterior vaginal pool. All specimens were obtained by one of the authors, who also noted any physical abnormality of the genital tract. After cleansing the vulva, a mid-stream specimen of urine was collected. Specimens were despatched to the laboratory and examined within 1 hour.

Swabs were cultured on blood agar in an atmosphere of 10% CO_2, on blood agar anaerobically, and on MacConkey agar aerobically. A wet preparation from the swab was examined for the presence of pus cells and *Trichomonas vaginalis*. Gram films were examined for bacteria and yeasts. Viable bacterial counts were performed on uncentrifuged urine by a standard loop technique, and a centrifuged urinary deposit was examined for pus cells.

Bacteria were identified by conventional methods. Lactobacilli, diphtheroids and coagulase-negative staphylococci were regarded as vaginal commensals; other organisms were considered to be potentially pathogenic. Coliform bacilli, *Proteus* and *Strep. faecalis* were specifically regarded as "potential urinary pathogens". *Candida albicans* was identified by germ-tube production and by agglutination with specific antiserum. Lancefield grouping was performed on all Beta-haemolytic streptococci.

The statistical significance of results was assessed by the chi-squared and Fisher exact tests, as appropriate.

Findings

The frequency of isolation of micro-organisms from the vagina and the relationship to diabetic, symptomatic and menstrual status are shown in Table I. 43 patients had a normal vaginal flora and no micro-organisms were isolated from the cultures in 7 women. From the remaining 40 patients (44%), 61 isolates of potentially pathogenic organisms were obtained. Quantitative aspects of the cultures are illustrated in Table II.

51% (27 of 57) diabetic patients were colonised by potential pathogens, as compared with 39% (13 of 33) of the non-diabetics. 27 patients, 16 diabetic and 11 non-diabetic, had colony counts of potential pathogens in excess of 50 colonies per plate. These differences were not statistically significant.

Table I

Vaginal Flora in Relation to Diabetes, Symptoms and Menstrual Status

		No. of isolates from patients in the categories shown					
Organism	Total isolates	Diabetic (57)[1]	Non-diabetic (33)	Symptomatic (59)	Asymptomatic (31)	Pre-menopausal (31)	Post-menopausal (59)
"Normal flora	43 (47)[2]	26 (46)	17 (51)	25 (42)	18 (58)	18 (58)	25 (42)
Coliforms	16 (18)	11 (19)	5 (15)	10 (17)	6 (19)	2 (6)	14 (24)
Proteus	9 (10)	6 (10)	3 (9)	6 (10)	3 (10)	1 (3)	8 (14)
Strep. faecalis	11 (12)	6 (10)	5 (15)	10 (17)	1 (3)	3 (10)	8 (14)
Beta-Haem. streptococci	10 (11)	9 (16)	1 (3)	8 (14)	2 (6)	2 (6)	8 (14)
Alpha-Haem. streptococci	2 (2)	1 (2)	1 (3)	1 (2)	1 (3)	1 (3)	1 (2)
Haemophilus	2 (2)	1 (2)	1 (3)	1 (2)	1 (3)	1 (3)	1 (2)
Staph. aureus	1 (1)	0	1 (3)	1 (2)	0	1 (3)	0
C. albicans	7 (8)	4 (7)	3 (9)	5 (8)	2 (6)	3 (10)	4 (7)
Trichomonas	3 (3)	1 (2)	2 (6)	3 (5)	0	1 (3)	2 (3)
No growth	7 (8)	4 (7)	3 (9)	4 (7)	3 (10)	2 (6)	5 (8)

[1] Figures in parentheses indicate number of patients in each category.

[2] Figures in parentheses indicate percentages.

Table II

Degree of Growth Obtained on Culture of Vaginal Swabs

		No. of cultures yielding	
Organism	Total isolates	< 50 colonies per plate	50 or more colonies
Coliforms	16	7	9
Proteus	9	4	5
Strep. faecalis	11	3	8
Beta-Haem. streptococci	10	4	6
Alpha-Haem. streptococci	2	0	2
Haemophilus	2	0	2
Staph. aureus	1	0	1
C. albicans	7	5	2

67% (6 of 9) of the patients with "good" diabetic control were colonised with potential pathogens, compared with 50% (10 of 20) and 46% (6 of 13) of those with "moderate" and "poor" control respectively. There was therefore no relationship between the degree of diabetic control, in the 42 patients eligible for assessment, and colonisation with potential pathogens.

Further analysis revealed that Beta-haemolytic streptococci were more frequently isolated from the diabetic patients (16%) compared with non-diabetic patients (3%) ($P < 0{\cdot}05$). Of the 9 isolates from diabetic patients, 5 belonged to group B, 3 to group C and 1 to group G. Four of the 5 diabetic patients carrying group B streptococci were poorly controlled, and 3 were insulin-dependent. The single isolate from a non-diabetic patient belonged to group G. There was no difference between diabetic and non-diabetic patients in the isolation of *C. albicans*, or of potential urinary pathogens.

Vaginal Flora in Relation to Symptoms, Menstrual Status and Sexual Activity

Of 59 patients complaining of urogenital symptoms, 30 (51%) were colonised by potential pathogens. This compares with 10 (32%) of the 31 asymptomatic patients. This difference was not statistically significant.

Bacteria potentially pathogenic for the urinary tract were isolated from 20 (34%) of the 59 post-menopausal patients, compared with 4 (13%) of 31 pre-menopausal women. When cultures with more than 50 colonies per plate were considered separately, it was found that only 2 (6%) of the pre-menopausal patients carried urinary pathogens, compared to 14 (24%) in the post-menopausal group. These differences were not statistically significant. Vaginal colonisation by Gram-negative bacilli or *Strep. faecalis* occurred in 16% (4 of 25) of patients aged between 20 and 39 years, increasing to 35% (8 of 24) and 29% (12 of 41) in those aged 40 to 59, and over 60 years, respectively.

No relationship was found between parity or sexual activity and the nature of the vaginal flora.

Variation of the Vaginal Flora with Time

Further vaginal swabs were obtained from 6 patients, once in 3 cases and twice in the remainder. One patient had a normal flora on 2 occasions. Two patients who carried coliforms were successfully treated with antibiotics for concurrent urinary infections; vaginal swabs examined subsequently revealed replacement of the coliforms by Beta-haemolytic streptococci in one, and by *Strep. faecalis* in the other. One woman carried *Haemophilus* in the vagina, and this organism persisted after a 10-day course of sulphonamides. Another patient had a heavy growth of *Staph. aureus* without clinical evidence of infection; spontaneous elimination had occurred 8 weeks later. A group B streptococcus in the remaining patient was still present after 1 week.

Laboratory Evidence of Clinical Infection

Pus cells were associated with the presence of potential pathogens in 16 patients. In 12 of these patients, the pathogen was the predominant organism in the culture. Pus cells were seen in the 3 patients with *Trichomonas vaginalis*, and in 6 of the 10 patients with Beta-haemolytic streptococci.

Abnormalities on Vaginal Examination

Vaginal examination was abnormal in 33 patients (37%). Atrophic mucosal changes occurred in 15 and vulvitis was seen in 22, 21 of whom complained of pruritus vulvae. 16 (73%) of those with vulvitis were diabetic, 8 being newly diagnosed and 3 poorly controlled. Bacteriological examination revealed a possibly pathogenic organism in the vagina in 13 cases. *Strep. faecalis* and *C. albicans* were the commonest organisms found, being isolated from 5 and 4 patients respectively.

Bacteriuria

Mid-stream urine cultures were obtained from 71 patients, 44 of whom were diabetic. Significant bacteriuria (more than 10^5 organisms per ml) was detected in 11 cases, all of whom were symptomatic and 7 diabetic. The incidence of bacteriuria was not significantly greater in the diabetic women. In the 10 cases where bacteriuria was due to Gram-negative bacilli, apparently identical organisms were recovered from the vagina. Only 6 of the 60 abacteriuric patients carried Gram-negative bacilli in the vagina. This represented a significant difference ($P < 0{\cdot}01$).

Discussion

This survey has confirmed the variability of the vaginal flora and its poor correlation with urogenital symptoms, and has revealed no significant difference between diabetic and non-diabetic women in these respects. While not reaching statistical significance, group B streptococci were more frequently isolated from the diabetics and were usually associated with the presence of pus cells in the vaginal secretions, the latter being considered the hallmark of vaginitis (Jeffcoate, 1967). Eickhoff *et al.* (1964) have reported an association between diabetes and infection by these organisms, and they have been particularly incriminated in neonatal and puerperal infections (Eickhoff *et al.*, 1964, McCracken, 1973). The vaginal carriage rate in diabetics has not previously been investigated, and our findings in this small survey suggest that further study is indicated.

The frequency of isolation of other bacteria was in close agreement with that reported by Morris and Morris (1967) in their study of non-diabetic women attending a family planning clinic. However these authors reported a higher incidence of *C. albicans* in the vagina than we encountered. The discrepancy may be due to the high proportion of post-menopausal women among our patients, since it is known that the vaginal secretions become alkaline after the menopause (Cruickshank and Sharman, 1934), and that such conditions are inhibitory to the growth of *C. albicans*. Although vulvitis is commonly ascribed to Candida infection, we discovered this yeast in the vagina of only 4 (18%) of our patients with vulvitis. Dawkins, Edwards and Riddell (1953), using more selective isolation measures, reported an incidence of Candida in the vagina of only 14%, during their extensive study of pre-menopausal women with vulvitis. In our patients, the finding of *C. albicans* in the vagina was not significantly greater in diabetics.

There has been increasing interest in the association between urinary infection and colonisation of the genital tract by Gram-negative bacilli and other enteric organisms (Stamey *et al.*, 1971). However, attention has largely centred on the flora of the introitus. Thus O'Grady *et al.* (1970) found a positive correlation between symptoms of the urethral syndrome and the presence of Gram-negative bacilli in the area immediately surrounding the external urethral meatus; some of their patients subsequently developed significant bacteriuria. Little attention has been paid to the relationship between urinary infection and high vaginal colonisation. The present survey suggests that this may be relevant since 10 of the 11 bacteriuric patients carried in their vagina organisms which were apparently identical with those isolated from the urine. This may merely reflect the fact that spread of organisms may occur from the introitus to the vagina as well as to the urinary tract; however it is also possible that established colonisation of the vagina with Gram-negative bacilli may make persistent or recurrent bacteriuria more likely. Study of a larger group of patients would be necessary for confirmation of this possibility.

Kass, Savage and Santamarina (1965) demonstrated that the prevalence of bacteriuria in females in the general populations of Jamaica and Wales rose with age by about 1% for each decade of life. In our pre-menopausal patients the prevalence of coliform bacilli and *Proteus* in the vagina was 6 and 3% respectively, figures which are in close agreement with those found for a similar group of patients by Morris and Morris (1967). However, following the menopause, colonisation of the vagina by Gram-negative bacilli showed a four-fold increase. Although our findings do not reach statistical significance, they suggest that the greater prevalence of Gram-negative bacilli with increasing age acts as a contributory factor in the development of bacteriuria in the post-menopausal woman.

Summary

The vaginal and urinary flora have been studied in 57 diabetic and 33 non-diabetic patients.

In both populations, no correlation was found between urogenital symptoms and colonisation of the vagina. There was no greater prevalence of potentially pathogenic organisms in diabetic patients, even when control was poor. However, although not statistically significant, group B streptococci were isolated more frequently from poorly controlled diabetics.

Bacteriuria was not significantly more common in diabetics.

Gram-negative bacilli were found in the vagina significantly more often in bacteriuric patients; the prevalence of such organisms being four-fold greater after the menopause.

We are indebted to Dr C. E. Davies for permission to study patients under his care, and to Dr R. A. Dixon for help with the statistical aspects.

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Short Case Report

Orbital Metastasis from Prostatic Carcinoma

In 1971, Schill described the eighth indisputable case of prostatic carcinoma with orbital metastasis. The symptoms usually produced by this tumour are diplopia and exophthalmos and the patient usually presents at the ophthalmological clinic. We report herein our experience on a patient presenting with gross haematuria and exophthalmos and who responded well to treatment with anti-androgenic hormone.

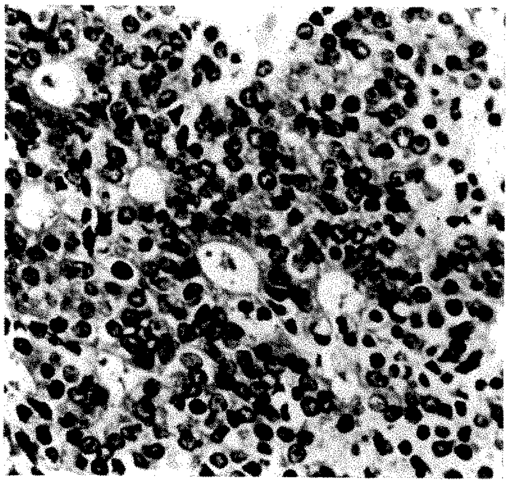
Case Report

A 79-year-old male was admitted because of diplopia and exophthalmos of the left eye. One month before, he had noticed gross haematuria which spontaneously disappeared. Physical examination revealed that the prostate was enlarged to about a hen-egg size, hard, irregular and fixed. The left eye felt abnormally firm on palpation and tonometry was 12·23 mm Hg on the right and 14·57 on the left which was disturbed at the upward movement of the eye-ball. Exophthalmos grade was 11·5 mm on the right and 23·5 mm on the left, respectively. X-ray examinations of the pelvis, vertebra and skull did not reveal any evidence of deposits, but IVP showed no excretion of dye by the left kidney. Acid and alkaline phosphatases were within normal limits. A perineal needle biopsy specimen, revealed a poorly differentiated adenocarcinoma of the prostate and open biopsy from the orbital space yielded adenocarcinoma identical to that of the prostate (Fig.).

On 23rd April 1969, the patient had a bilateral orchidectomy, and his course was one of good regression with exophthalmos grade of 20·0 mm and improved movement of the left eye 7 days later. He was then started on anti-androgenic hormone treatment with a total dosage of 10·5 g of stilboestrol diphosphate given 0·5 g per day by intravenous infusion and thereafter 60 mg of estradiol benzoate per day given by mouth. Exophthalmos grade of the left eye was well improved, *i.e.* 17·0 mm Hg on 14th May, 15·0 mm Hg on 27th May. With slight deviation of the left eye, he was discharged on 4th June 1969 but died with pneumonia on 10th December, 1969.

Comment

Albert *et al.* (1967) found metastasis to the eye or orbit in 2·3% in their necropsy series of 213 adult patients with known primary tumours. The most common primary neoplasms in cases with metastasis to the eye were breast and lung. As far as we know, only 8 cases with primary prostatic carcinoma have been reported till now. One case was treated with radiation (Bard and Schulze, 1962), and 6 were treated with anti-androgenic hormone; a good response was obtained from 4, including our case (Harper, 1963; Schill, 1971).



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The Nitrofurans as Sperm Immobilising Agents: their Tissue Toxicity and their Clinical Application

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Freund and Davis (1969) have shown that the disappearance rate of sperm following bilateral vasectomy and azoospermia can be predicted by an exponentially decreasing curve. Marshall and Lyon (1972) examined 200 cases of vasectomy, analysing every fourth ejaculate postoperatively. After 12 ejaculations only 65·5% of the patients were sperm-free. After 24 ejaculations 2·5% of the patients still had sperm in their seminal fluid.

Although Freund and Davis noted a 35% decrease in the sperm count from the patient's previous ejaculate, Marshall and Lyon noted that more than 10 ejaculations were necessary to reach azoospermia in 35% of their cases. They also found that younger and sexually active patients cleared their ductal reservoir of sperm with fewer postoperative ejaculations.

Vas irrigations with water have been used by Craft and McQueen (1972) at the time of vasectomy to reduce their postoperative sperm counts. They were successful in decreasing the sperm counts from 34% at 12 weeks postoperatively in the non-irrigated patients to 16% with positive counts in the irrigated group. Urquhart-Hay (1973) has successfully used euflavine solution as a vas irrigant to achieve immediate postoperative sterility in 81 patients. By irrigating the vas deferens with a sperm-immobilising solution, sterility would be attained in the immediate postoperative period.

Prior and Ferguson (1950) demonstrated that certain nitrofuran compounds have the ability to depress spermatogenesis in rats. Nelson and Steinberger confirmed this in 1952 and found that nitrofurans halted spermatogenesis at the primary spermatocyte stage. Dokov and Timmermanns (1970) have shown that nitrofurans also cause metabolic alterations in the spermatogonium and interstitial tissue enzyme concentrations. Nelson and Bunge (1957) have reported that Furadantin given orally (in humans) in doses of 10 mg/kg/daily may produce temporary spermatogenic depression.

Our work involved the investigation of the nitrofurans (more specifically, nitrofurantoin sodium and nitrofurazone) as sperm-immobilising agents, and evaluation of their tissue toxicity and their possible application in conjunction with vasectomy.

Materials and Methods

Part I

Using calibrated droppers, varying concentrations (from 0·5 mg/ml to 40 mg/ml) of nitrofurantoin sodium and nitrofurazone were incubated with freshly ejaculated human spermatozoa at 37°C. Percentage motility of the solution was then assessed at 5-, 10-, 20- and 30-minute intervals and compared to control solutions comprised of spermatozoa and saline of matched concentrations assessed at the same intervals. A total of 24 ejaculates were analysed from different donor sources.

Part II

Tissue toxicity studies were performed using 36 sexually mature Hartley strain male guinea-pigs. Under Nembutal anaesthesia intraperitoneally given on a weight basis, the guinea-pig's scrotal area on one side was shaved with animal shears and prepped with betadine solution. A 2-cm upper scrotal incision was made. The subcutaneous tissue was divided by blunt dissection and the testis in its coverings was then delivered into the operative field. The vas deferens was then isolated between two 3-0 Tewdek ligatures and an incision was made at a 45° angle to the vas with a fine iris scissors and the vas was cannulated with PE 50 Teflon catheter. The distal vas deferens was then flushed with a solution of nitrofurantoin sodium and/or nitrofurazone in a concentration 3 times greater than is necessary to obtain sperm immotility *in vitro*. The vas was then divided and the distal vas was anchored to the perivasal tissues for later identification. The incision was closed with a 2-0 chromic interrupted suture. At intervals of 1, 2, 4, 6, 8 and 12 weeks the guinea-pigs were sacrificed and their vasa were completely dissected. Specimens were sampled at different levels of the flushed distal vas segment. These were studied histologically and compared to the non-operated control side.

Results

Part I

Nitrofurantoin sodium was found to be sperm-immobilising in the minimum concentration of 20 mg/ml while nitrofurazone exhibited a similar effect at 1 mg/ml. The controls, however, revealed no loss of motility during the same time intervals examined (Tables I to IV). All results were found to be consistent in the 5 : 1 and 10 : 1 sperm dilutions.

Table I

Effect of Nitrofurantoin Sodium on Human Spermatozoa *in vitro* at 37°C. 5 : 1 Dilution

	5 min	10 min	20 min	30 min
5 mg/cc	50%	50%	40%	20%
10 mg/cc	40%	40%	30%	20%
20 mg/cc	0	0	0	0
40 mg/cc	0	0	0	0
Control	>50%	50%	45%	45%

% = Percentage motility.

Table II

Effect of Nitrofurantoin Sodium on Human Spermatozoa *in vitro* at 37°C. 10 : 1 Dilution

	5 min	10 min	20 min	30 min
5 mg/cc	45%	40%	30%	20%
10 mg/cc	40%	30%	30%	25%
20 mg/cc	0	0	0	0
40 mg/cc	0	0	0	0
Control	>50%	50%	45%	45%

% = Percentage motility.

Part II

Histological sections consistently revealed that nitrofurantoin sodium and nitrofurazone were non-toxic to the vas deferens when used in concentrations up to 3 times greater than necessary for sperm immobilisation. There was no evidence of any vasal or perivasal inflammation at the earlier intervals. There was also no evidence of any delayed inflammatory or granulomatous vas resection in the later specimen groups.

Table III

Effect of Nitrofurazone Solution on Human Spermatozoa *in vitro* at 37°C. 5 : 1 Dilution

	5 min	10 min	20 min	30 min
0·5 mg/ml	25%	20%	15%	10%
1 mg/ml	0	0	0	0
2 mg/ml	0	0	0	0
Control	60%	50%	50%	50%

% = Percentage motility.

Table IV

Effect of Nitrofurazone Solution on Human Spermatozoa *in vitro* at 37°C. 10 : 1 Dilution

	5 min	10 min	20 min	30 min
5 mg/ml	25%	20%	15%	15%
1 mg/ml	0	0	0	0
2 mg/ml	0	0	0	0
Control	>60%	50%	50%	50%

% = Percentage motility.

Conclusion

Our experiments have shown that the nitrofurans have the capability of causing sperm immobilisation when utilised in certain critical concentrations. Both drugs were also known to be non-toxic to the vas deferentia in concentrations exceeding that necessary to attain their immobilising effect (Albert *et al.*, unpublished findings).

Clinical Application

Clinically, our findings have broad potential applications in the area of male reproductive physiology. Since these two nitrofurans have been shown *in vitro* to be sperm immobilising and have not exhibited any deleterious toxic effects to the vas or perivasal tissues, it is a logical extension that these drugs could be used as an intraoperative flush as an aid in producing a more rapid disappearance rate of sperm post vasectomy.

Procedure

Vasectomy was performed as an out-patient procedure in 24 patients in the following manner:

The vas was isolated from the other elements of the cord, held between the thumb and forefinger and 1% lignocaine was infiltrated over the vas and skin surface. An incision was made directly down the vas deferens which was then secured with an Allis clamp. After the adventitia had been dissected away, 3 to 4 cm of vas was then exposed. The testicular side was then occluded with two Weck clips, and a longitudinal vasotomy incision was then made in the upper vas deferens. The vas was catheterised with a PE 50 Teflon catheter, which was then advanced 2 cm attached to a 6 ml syringe filled with nitrofurantoin and/or nitrofurazone solution and each side flushed with 3 cc of the solution. The catheter was then removed, a 1-cm of vas excised, and the upper vas occluded with 2 Weck clips. The wound was closed in a single layer of 3-0 interrupted chromic. There were no untoward reactions to the vas irrigations; in particular, there was no evidence of any vasitis.

The initial 2 consecutive postoperative ejaculates were examined within the first week after vasectomy. Semen specimens were later examined at 6 months and 1 year after operation to ensure that spontaneous reunion had not occurred. All specimens were examined immediately upon their receipt and also after a 10-minute period of incubation. No live spermatozoa were found in any of the specimens.

Comment

The irrigation procedure adds little time to the standard vasectomy and can easily be performed as an out-patient procedure.

It minimises time-consuming postoperative sperm analyses. In underdeveloped countries where postoperative follow-up examinations are more difficult to obtain, this procedure would provide an additional positive factor in an attempt to ensure sterility.

Summary

Nitrofurantoin sodium and nitrofurazone in certain critical concentrations have the ability to cause sperm immobilisation.

Intraoperative vas irrigation with these solutions in 24 patients have produced sterility in the immediate postoperative period.

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Short Case Report

Artificial Penile Nodules: Case Reports from Thailand

There have been two reports of embedding of beads into the penis in the Argentinian urological literature (Grimaldi, 1953; Grimaldi, 1954). The purpose of this paper is to present 16 cases of the artificial penile nodules (APNs) incidentally seen at the Skin Clinic of the Bhumibol Adulyadej Hospital since 1970.

Case Reports

The histories and clinical lesions of all 16 cases were essentially similar and will therefore be summarised for brevity.

All were young men of normal mentality, ranged in age from 21 to 30, and encouraged to have beads embedded into the penis for psychosexual reasons. They had had the artificial penile nodules for a variable period of time ranging from months to 10 years without symptoms. There was neither dysuria nor pain at the time of erection and intercourse. Urination, erection and ejaculation of semen were not interfered with by the APN.

On examination, one or more subcutaneous nodules were found on any area usually dorsum of the penis. The shape of each nodule was round and its size was about 1 cm in diameter. It was hard and non-tender to palpation, and moved after preputial retraction. The overlying skin and surrounding area were normal. Roentgenographic examination showed small, round, radiopaque shadows of the nodules in the penis. All except case 5, in which a bead was found in a white fibrous capsule in the superficial fascia of the penis, refused surgical removal of the beads.

Discussion

Embedding of one or more beads into any area but usually the dorsum of the penis for the purpose of increasing coital excitation and orgasm of the mate is a common procedure, usually done by unqualified personnel in prisons and certain places of low socioeconomic groups of people of Thailand. The layman technique of the procedure is as follows: a selected area on the penis was pierced by a sharp pointed instrument without local anaesthetic. A bead, which had been kept in tincture of iodine for 24 hours, was then immediately inserted into the superficial fascia of the penis. Multiple beads up to ten may be embedded into the penis by this method. Most beads were derived from the bottom of Tancho pomade glass jars and a few came from various stones. It has been said that others such as bullets, paddies, pearls and jewels may be used to produce the APNs.

In psychosexual points of view, all 16 cases reported herein were obviously of normal mentality and without sexual inferiority complex. They were encouraged to have the APNs by friends. With regard to roentgenological diagnosis, a radiopaque shadow of the APN must be differentiated from that of urethral or vesical calculi, and of a retained bullet. In dermatology, an APN must be differentiated from sclerosing lipogranuloma, paraffinoma, silicone granuloma, cyst, mucocele, and calcification or ossification of the penis; and from penile nodules due to subacute angiitis (Rubenstein and Wolff, 1964). The characteristic glassy or stony hardness of the lesion and a history of prior embedding of one or more beads into the penis are helpful in making the diagnosis of the APN.

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I am most grateful to Air Vice-Marshal Noi Panikbutr for permission to report these cases; and to Wing Commander Kitti Yensudchai, for performing surgical removal of the APN (case 5).

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Short Case Report

Spermatogenesis following Bilateral Orchidopexy in Adult Life

Case Report

Undescended testicles were first noticed in this patient at the age of 16 years and semen analysis had shown no spermatozoa. When seen in 1969 aged 22 years, physical examination showed that both testicles were ectopic and lying in the superficial inguinal pouch. The organs were well developed but would only descend as far as the neck of the scrotum, which was itself underdeveloped. Seminal analysis again showed azoospermia.

Subsequently bilateral Ombrédanne orchidopexies were performed. Seminal analysis was carried out 4½ months and 5 months after the operation. The first specimen showed 7×10^6 sperms/ml with retarded liquefaction and sluggish motility and the second specimen contained 5×10^6 sperms/ml with complete liquefaction and 30% motility at 3 hours. Half the spermatozoa in the second specimen were normal in structure.

6 months after operation the patient was accidentally killed. Post-mortem histology of both testes showed active spermatogenesis.

Comment

Degenerative changes with absent spermatogenesis are usually demonstrable in the testes of men who reach adult life with bilateral cryptorchidism (Johnston, 1968), although there are a few reports of patients with maldescended testes, active spermatogenesis and even successful paternity (Hand, 1957). The lower environmental temperature of the scrotal position is essential for spermatogenesis (Moore and Quick, 1924) and this may explain the onset of active spermatogenesis in this patient following operation, in whom the testicles were otherwise normal. Orchidopexy after puberty may, therefore, be worth while on occasion.

Acknowledgement

I am grateful to Mr R. S. Murley for permission to publish this case.

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ABSTRACTS FROM CURRENT UROLOGICAL LITERATURE

Surgery, Gynecology and Obstetrics

By THOMAS MOORE

"Caval Umbrella to trap Emboli in Patients with Renal Cell Carcinoma." R. M. FARRELL, J. BLOCH and V. F. MARSHALL. (1974, **139**, 835-839.)—The authors from the Departments of Urology and Thoracic Surgery, Cornell University Medical College, New York, state that renal cell carcinoma involves the inferior vena cava in 5 to 10% of cases. In spite of this, some patients still apparently can be cured by surgery. They report a case of a 46-year-old male suffering from anaemia and loss of weight shown by clinical and the necessary special investigations to be due to a large carcinoma of the left kidney with almost complete occlusion of the abdominal portion of the vena cava with extensive collateral circulation. No distal emboli could be demonstrated by pulmonary tomograms and arteriograms, liver and lung scans and general skeletal radiological survey. At exploratory laparotomy the lesion was found to be resectable. They describe in detail the operation carried out for the radical removal of the kidney, the clot and neoplasm from the lumen of the vena cava and the part of its wall directly invaded by the tumour. During the procedure a pulmonary by-pass and an umbrella filter in the cardiac orifice of the vena cava were used during the appropriate parts of the operation. 18 months after operation, apart from a ventral hernia, the patient was symptom free but later developed cerebral metastases. With modern techniques, the authors stress that the by-pass is a safe procedure.

"Ureteropelvic Obstruction in Children." HORST ZINCKE, PANAYOTIS P. KELALIS and ORMOND S. CULP. (1974, **139**, 873-878.)—From the Mayo Clinic the authors present the clinical features, diagnosis and treatment of the uretero-pelvic obstruction culled from the records of 152 children. The main presenting symptoms were pain, haematuria and unexplained fever. The most useful diagnostic technique was infusion urography. Of 172 operations performed, 121 were some form of pyeloplasty. Simple ureteropyelostomy (excision of a minimal amount of pelvis and ureter with end to end anastomosis after spatulation of the end of the latter without the use of any splints) was the most effective and popular operation and gave the best results. 10 pyeloplasties which were failures included the only 3 by the Hynes-Anderson technique, but these were in very complicated cases. In 25 patients the obstruction was bilateral. Nephrectomy because of the advanced stage of the disease was carried out in 41 patients.

"Experience with Living Familial Renal Donors." ALAN HUGH BENNETT and J. HARTWELL HARRISON. (1974, **139**, 894-898.)—The authors report from the Peter Bent Brigham Hospital, Boston, where the first successful transplantation of a kidney from a living donor was performed on 23rd December 1954. From that time until July 1973, 300 living related donor nephrectomies have been performed. After successful histocompatibility tests, nearly 30% of possible donors have been rejected because of previous unrecognised medical or psychiatric problems or renal vascular abnormalities, which would make nephrectomy or successul transplantation technically difficult. One candidate was found to have, during the evaluation, a renal cell carcinoma. The authors state that this has been reported in other centres and in one, only after donor nephrectomy had been performed. During the last 5 years more elderly donors, the oldest 80 years, have been accepted. A 76-year-old woman donor died from fulminating postoperative hepatic necrosis due to halothane induced hepatitis. 9 donors were aged 21-30 years, 55, 31-40 years, 56, 41-50 years, 86, 51-60 years, 67, 61-70 years, 25, 71-80 years and 4, 80 years. The average age was 44·6 years. 156 were men and 144 were women. 9 minors donated a kidney to their identical twins. In 7% the donor and recipient were identical twins, 51% siblings, 44% parents, 2% offspring and 6% more distant relations. Only 1 unrelated donor was used early in the series. After complete investigation 251 donors were found to be healthy. 49 had abnormalities not sufficient to contraindicate donation, which included 12 with chronic pulmonary disease, 11 with significant hypertension, 9 with recurrent cystitis, 3 with inactive pyelonephritis, 6 with obesity, 4 with diabetes, 1 with recurrent vesical papillomata, 2 with inactive tuberculosis and 1 with Parkinson's disease. 3 serious postoperative complications occurred among these; a 60-year-old woman with hypertension, obesity and recurrent cystitis developed a severe wound infection which took 6 months to heal, another hypertensive donor developed a serious psychosis and another with recurrent cystitis, 3 years after donation developed pyelonephritis in the remaining kidney. From their extensive experience the authors give much useful advice not only on the technique of removal of the kidney from the donor, but also on its transplantation to the recipient and discuss the postoperative mental reactions of both donors and recipients.

"The Relationship of Genitourinary Tract Procedures and Deep Sepsis after Total Hip Replacements." ROBERT IRVINE, B. LAMAR JOHNSON and HARLAN C. AMSTUTZ. (1974, **139**, 701-706.)—The authors at the University of California, Los Angeles, have carried out very detailed investigations of the bacterial content of the air in a conventional theatre and one with a directed horizontal filtered airflow system. They have shown that the latter reduces by 7-fold the bacterial theatre air counts. They have also shown, in a study of 8 total hip replacements carried out in each type of theatre, that deep infections are usually due to Gram-negative organisms, often associated with unrecognised infections of the urinary tract.

"Renal Arteriovenous Fistulas." DAVID P. O'BRIEN, III, THOMAS S. PARROTT, KENNETH N. WALTON and ERNEST L. LEWIS. (1974, **139**, 739-743.)—The authors from Atlanta, Georgia, report a personal series of 7 cases, which brings the total now reported in the literature to 225. The common aetiology is either congenital, where the aneurysm is of the cirsoid type, or acquired, in which needle biopsy and trauma now play the leading part although neoplasms may cause such a fistula. Clinically haematuria, hypertension and an audible bruit in the abdomen or loin are the presenting features. Renal arteriography is the essential diagnostic tool and the site of the fistula can thus be localised. Although attempts at renal arterial reconstruction are usually not possible, partial nephrectomy may sometimes be feasible. Of the 7 cases reported, 4 were treated by nephrectomy, 2 by partial nephrectomy and 1 conservatively. The latter routine is recommended for those following needle biopsy.

"Late Results of Intubated Ureterotomy." STEFAN WESOLOWSKI and ANDRZEJ BORKOWSKI. (1974, **139**, 578-584.)—Between January 1961 and December 1971 the authors at the Warsaw Medical Academy carried out 193 such operations on 179 patients. Follow-up examinations were carried out on 100 patients who were classified into 3 groups according to the type of obstruction.

1. The first operation for hydronephrosis.
2. The second operation for hydronephrosis.
3. Cases associated with stones with primary or secondary hydronephrosis.

In 76 patients results were regarded as good, in 16 satisfactory and poor in 8. The authors discuss the indications and results in each group, these are best in the third. Details of their technique and the method of splintage are included.

La Nouvelle Presse Médicale

By JOHN GRIEVE

"Difficulties in the Diagnosis of Renal Tumours by Arteriography—Experience with 150 Cases." J. L. LAMARQUE, W. JASPART, J. P. SENAC and J. PASQUAL (Montpellier). (1974, **3**, 2229-2232.)—With careful technique the authors have found renal arteriography a reliable diagnostic aid. The chief problem has been when a tumour was vascular but apparently benign. Experience using drugs such as angiotensin has not been sufficient to report as yet. Needle biopsy is suggested in cases of doubt before surgical exploration.

"Lumbo-aortic Lymph Node Involvement in Testicular Teratoma." J. C. DURAND and F. BARRAT. (1974, **3**, 1929-1932.)—The authors did 61 block dissections of the lumbo-aortic nodes in patients with testicular teratoma and found 30% involved though clinically latent. In the absence of macroscopic evidence of involvement a unilateral block dissection was considered adequate, Lymphography was unhelpful with 44% of false negatives. The overall 3-year survival was 65% (50% when node invasion was present and 80% when there was no involvement).

"Familial Carcinoma of the Kidney and the H.L.A. System." M. VALLETEAU DE MOÚLLIAC, R. GANANSIA, J. HORS, A. LETEXIER and M. MORIN. (1974, **3**, 1539-1542.)—In a family of 7, 2 brothers and 2 sisters all developed cancer of the left kidney in middle life. All four were neoplasms with eosinophilic cells, diagnosed at a late stage and showing widespread lymph node involvement. These findings led to genetic studies in the family. HLA typing showed that 2 were of similar type and 4 were identical. The authors wonder if the genotype HLA-2 HLA-12 is a factor predisposing this family to renal cancer.

Der Urologe

By JOHN GRIEVE

"Breast Carcinoma in a Patient having Oestrogen for Prostate Carcinoma." H. BÜLOW, H. K. WALLSTEIN, G. BÖTTGER and F. H. SCHRÖDER. (1973, **12**, 249-253.)—A 64-year-old man with adenocarcinoma of the prostate had 12 g of Honvan infused over a period of 10 days followed by a transurethral resection of the gland (October 1971). Postoperatively he was treated with polyoestradiol phosphate 80 mg as a depôt dose and 40 mg monthly thereafter. He developed gynaecomastia in May 1972 and in July 1972 a carcinoma of the right breast with axillary node involvement. Mastectomy with lymph node dissection was followed by radiation and in December 1972 he he was apparently well. The authors draw attention to 30 similar cases in the literature.

"How dangerous is Transurethral Splitting of the Ureteric Orifice for Intramural Stones?" P. GEERING, G. RUTISHOUSER, P. GRABER and M. ELKE. (1973, **12**, 292-294.)—Among 43 patients who had the ureteric orifice slit transurethrally 34 were followed up. In 10 patients there was vesico-ureteric reflux and in this group pyelonephritic episodes were 5 times more common than in those without reflux. The authors believe that an incision greater than 5 mm is regularly followed by reflux.

"Diagnosis and Operative Treatment of Distal Stenosis of the Female Urethra." J. G. MOORMAN, H. B. KAS and R. BRAUSCH. (1974, **13A**, 213-216.)—Over 200 girls aged 4-15 years with distal urethral stenosis have been examined and treated. Calibration was with bougies à boule. The authors used operative urethrotomy rather than dilatation and had good results in the majority of their patients.

"Subtotal Replacement of the Urinary Bladder by Whole Human Cranial Dura Mater." E. SCHMIEDT, P. CARL G. STAEHLER and K. WANNER. (1974, **13A**, 228-231.)—In 2 patients in whom sub-total cystectomy was performed for bladder carcinoma the vault of the bladder was replaced by rehydrated preserved human cranial dura mater. Follow-up over a period of months has shown remarkably good bladder function. In the second patient radiograms 9 months after operation show a very normal looking bladder outline.

Deutsche Medizinische Wochenschrift

By JOHN GRIEVE

"The Activity of γ Glutamyl Transpeptidase in 24 Hour Urine Collections in Different Types of Renal Disease." G. BAHRE, R. KLEY and H. BRASS. (1974, **99**, 2214-2218.)—The γ glutamyl transpeptidase activity was measured in 24 hour urine collections from 89 patients with differing forms of renal disease. In 11 patients with acute or chronic glomerulonephritis but no renal failure the activity was significantly raised while in 13 patients with chronic glomerulonephritis and in renal failure the activity was markedly reduced. A further 30 patients with tubulo-interstitial disease showed reduced levels regardless of whether renal failure was present or not. In general terms patients with renal disease and renal failure showed a reduction in activity roughly proportional to the severity of the disturbance of function. An exception was during the repair phase of acute renal failure when urinary enzyme activity was increased.

"Extra-osseous Metastases from Prostatic Carcinoma." P. WEBER, H. OESER, V. TAENZER, H. ROST and A. KELAMI. (1974, **99**, 2148-2150.)—In 80 cases of prostatic carcinoma lymphography suggested much earlier spread of the neoplasm by the lymphatics than has been customarily believed. Clinical pulmonary metastases were rare but not uncommon at autopsy. The authors suggest that hormone treatment may retard extra-osseous metastatic growth thus making osseous metastases more prominent clinically. (This seems in many respects a non-sequitur. In the circumstances it is more probable that the host-neoplasm relationship is important.)

"Urological Operations in Patients with Haemophilia." H. KLOSTERHALFEN, M. W. KOLLERMANN, A. KURME, D. PLESSOW and H. BUSCH. (1974, **99**, 2095-2098.)—In 6 patients with haemophilia it has been possible to achieve a progressive reduction in the operative risk by careful control at all stages of the factor VIII and IX substitution. It is unwise to attempt surgery without close collaboration with a specialist laboratory.

"Fertile Eunuchoidism (Pasqualini Syndrome)." O. P. HORNSTEIN, H. BECKER, N. HOFMANN and H. P. KLEISSL. (1974, **99**, 1907-1914.)—A shift in the FSH-ICSH relationship corresponding to early pubertal development has been shown in 3 patients with fertile eunuchoidism by radio-immuno-assay for plasma ICSH and FSH and by testicular biopsy. Intravenous injection of 100 μg of LH releasing hormone caused prompt liberation of large quantities of ICSH showing that the failure was at hypothalamic level rather than pituitary. A fourth patient had a markedly delayed and retarded puberty suggesting a temporary Pasqualini syndrome while a fifth had a reduction in ICSH excretion following a cerebral contusion.

"Diagnosis of the Site of Adrenal Tumours by Ultrasound." K. D. MORGNER, P. OTTO, H. J. WEDEMEYER and D. TOLLNER. (1074, **99**, 1519-1521.)—Ultrasound has been used in 8 patients to demonstrate the presence of a tumour in the adrenal gland. When the tumour is 3 cm in diameter the results are reliable. The technique is simple and can be used repeatedly without danger to the patient.

"Localisation of Parathyroid Adenomas in Primary Hyperparathyroidism by Selective Parathormone Estimations." G. OFFERMAN, A. OPITZ and R. SÖRENSEN. (1974, **99**, 1308-1312.)—These authors state that the venous drainage from parathyroid adenomas is via the thyroid plexus. The flow into the great veins of the neck is unilateral and mainly in the right and left inferior thyroid veins. Parathormone concentration was measured by radioimmunoassay of samples selected from the thyroid and neck veins. In primary hyperparathyroidism differing concentration indicated the localisation of the adenoma before operation. Surgery confirmed these findings. Secondary parathyroid hyperplasia produced a bilateral increase in parathormone thus differentiating this from the solitary adenoma. These assays are of most value when there has been a previous negative exploration.

"The Effect of a Single Daily Dose of 300 mg of Allopurinol on Serum Uric Acid Concentration and Urate Excretion in Gouty Patients." F. MATZIES and G. BERG. (1974, **99**, 2464-2465.)—A single daily dose of 300 mg of allopurinol in the morning reduced the serum uric acid concentration and urate excretion within 6 days. This becomes a possible system of treatment of diseases where serum uric acid levels are raised.

Journal de Chirurgie

By JOHN GRIEVE

"Needle Nephrostomy." J. C. MASSON and CL. BOLLACK. (1974, **107**, 409-420.)—These workers from Strasbourg describe simple technique of nephrostomy using a needle to introduce the catheter. They report 6 cases successfully managed in this way—4 cases of carcinoma cervix, an ovarian tumour and a case of neoplastic retroperitoneal fibrosis. In some patients the anuria then resolved spontaneously while in others a definitive form of treatment *e.g.* cutaneous ureterostomy could be performed later.

Zeitschrift für Urologie

By JOHN GRIEVE

"The Problem of Urolithiasis in Childhood." C. SCHMECHEL and J. SCHUBERT. (1974, **67**, 495-501.)—The authors report on 84 children who had urinary stones removed. In 35% of the children removal of the stone was accompanied by a plastic operation on the urinary tract. Follow-up time in 79 of the children averaged 6 years and the recurrence rate was 22%. Most recurrences came within 4 years of operation but some were as late as 10 years. Urinary infection encouraged recurrence. For long-term management the authors recommend (1) early operative removal of the stone and correction of any anomaly of the urinary tract and (2) long-term chemotherapy for infection (N.B. the table with data about stone composition is very sketchy).

Urologija i Nephrologija

By VICTOR LANE and ANTON PYTEL

"Long Term Treatment of Patients with Primary Chronic Pyelonephritis." O. L. TIKTINSKY. (1974, **5**, 3.)—This regime consists in giving a succession of antibiotics for 3 weeks of each month; during the remaining week, diuretics and antiseptics are prescribed. The course is continued for 1½ to 2 years. Benefits are reported to include (1) Reduction in the incidence of exacerbation; (2) Diminution in the amount of pyuria in 42·7% of cases, with normal urine being restored in 16·7%.

"Diagnosis and Treatment of Solitary Renal Cysts." A. YU. BAKHU. (1974, **5**, 20.)—The observations are based on a series of 129 patients seen between 1954 and 1973 in the Moscow 2nd Medical Institute. 61% presented with pain, 49% having haematuria and a palpable mass could be felt in 36%. Only 22% were asymptomatic. A study of the intravenous urogram in 36 patients did not make it possible to exclude neoplasm whereas renal angiography showed that in 20 of these the lesion did consist of a cyst; in 6 patients the diagnosis was established by puncture of the cyst. 116 patients in the series were operated upon, nephrectomy being performed in 28 and conservative procedures in the others. The largest cyst contained 6 litres of fluid.

"Results of TUR of the Prostate in a Series of 700 Patients." A. SHKODNY. (1974, **5**, 45.)—During a period of 4 years in Katowice, 700 patients with prostatic obstruction were treated by transurethral resection irrespective of the size of the gland. The procedure should not last more than 45 minutes. Only 3 patients died (0·4%), 4 patients had partial urinary incontinence and in 3 the prostatic capsule was perforated. The author concludes that this is the safest method of prostatectomy, but there is no reference in the paper to the amount of tissue resected.

"Chronic Prostatitis and Carcinoma of the Prostate." V. A. GLADKOV. (1974, **5**, 54.)—In 103 patients with chronic prostatitis, transrectal biopsy was carried out on 119 occasions to exclude the possibility of coincident carcinoma. Adenocarcinoma was noted on 5 occasions and a poorly differentiated neoplasm once.

The Australian and New Zealand Journal of Surgery

By J. P. MADDERN

"Secondary Surgical Intervention in Acute Renal Failure." VERNON MARSHALL. (1974, **44**, 96-101.)—The author reviews a series of 118 patients with post-operative acute renal failure occurring at the Royal Melbourne Hospital between 1959 and 1973. Urological and vascular operations accounted for 33 of these patients while abdominal surgery was followed by renal failure on 42 occasions. The renal failure was usually the consequence of a major, although sometimes occult complication of surgery. The renal failure was associated with post-operative hypotension and collapse. Abdominal pains and signs of peritonitis were often slight or absent. In this series medical causes such as coronary occlusion and pulmonary embolus were seldom encountered and Gram-negative septicaemia as a primary cause of the collapse was seldom substantiated. Early abdominal re-exploration was often required and benefited the patient. When peritoneal contamination was found, establishment of free drainage, excision of necrotic tissue and peritoneal lavage was instituted. The value of peritoneal lavage was stressed by the author, particularly in patients with pancreatitis and diffuse intra-abdominal sepsis. Despite early surgical intervention the mortality was high accounting for 50% of the group of patients.

"Delayed Rupture of the Ureter." K. J. HARDY, E. S. R. HUGHES and J. C. B. PENFOLD. (1974, **44**, 137-139.)—The authors describe two cases of late ureteric fistula. In each patient the fistula developed 7 days after a second large bowel resection for recurrent carcinoma. The rupture occurred at the pelvic brim and in one case a nephrectomy was required, whilst in the other spontaneous cessation of urinary drainage occurred 7 weeks after the fistula developed. The authors stress the importance of maintaining the blood supply to the ureter during large bowel surgery.

"Giant Intraabdominal Seminoma: Case Report with a Brief Review of the Literature." N. V. RAGHAVAIAH, B. S. RAO and S. S. REEDY, Jr. (1974, **44**, 147-148.)—The authors report from the Department of Surgery, Andhra Medical College, Visakhapatnam, India a large seminoma of the testis which presented as an abdominal tumour with the dimensions of 25 cm × 20 cm × 15 cm weighing 1,550 g. The authors claim this to be the largest intra-abdominal seminoma reported in the literature.

"Epididymal Tuberculosis: An Unusual Presentation." N. V. RAGHAVAIAH. (1974, **44**, 149-150.)—The author reports from the Department of Surgery, Andhra Medical College, Visakhapatnam, India a primary epididymal tuberculosis presenting unusually as a cold abscess in the suprapubic region.

"Renal Allotransplantation in the Rat: Method and Histological Findings." R. W. BLAMEY, THELMA J. BAXTER, B. MCC. O'BRIEN and R. C. BENNETT. (1975, **44**, 179-192.)—A method of performing and assessing renal allografts in the rat is described by workers from St Vincent's Hospital, Melbourne. With this technique one kidney of the recipient is left *in situ*, whilst the other is replaced by an allograft. The degree of rejection of the kidney is histologically assessed and the changes with each grade of rejection are described whilst the changes of ischaemic necrosis seen in advanced rejection are also discussed.

"A Comparison of Perfusates for 24-hour Preservation of Ischaemically Damaged Canine Kidneys." J. MALCOLM DRUMMOND and A. G. R. SHEIL. (1974, **44**, 183-185.)—In this work which was carried out in the Department of Surgery of the University of Sydney a brief perfusion of ischaemically damaged canine kidneys was carried out with 3 separate solutions before a 24 hours' preservation in ice and subsequent autotransplantation. Using plasma-red-cell mixture, intracellular electrolyte solution (Collins C3) and extracellular electrolyte solution the authors were unable to find any significant superiority for any of the 3 solutions, all of which gave results similar to a control group in which no perfusion was carried out.

"The Prevention of Acute Tubular Necrosis in Renal Transplantation by Chronic Salt Loading of the Recipient." SHERMAN J. SILBER. (1974, **44**, 410-412.)—Noting that continuous salt loading had been shown to protect experimental animals remarkably against acute ischaemic tubular necrosis the author presents experiments to identify if this protection is intrinsic to the kidney, or involves the host. Kidneys were transplanted from salt-drinking rats to water-drinking rats and vice versa. The recipients were injected with glycerol to produce myohaemoglobinuric renal failure. The kidneys transplanted into salt-drinking animals did not develop acute renal failure provided that the animals had been given continued forced saline drinking for a considerable time prior to the transplantation. The author suggests that the experiments indicate that the protection afforded by a chronic salt loading is mediated by an effect upon the host rather than upon the kidney itself.

"A Comparison of Cryoprecipitated Plasma and Albumin Solutions for Machine Preservation of Ischaemically Damaged Canine Kidneys." A. G. R. Sheil, J. M. Drummond, G. E. Kelly, J. Boulas and D. C. Mears. (1974, **44**, 412-414.)—Before embarking on machine preservation of human kidneys for transplantation in the Department of Surgery at the University of Sydney the authors performed experiments on dogs to compare the efficacy of 4 solutions used in the perfusion of canine kidneys. Their findings were that canine cryoprecipitated plasma and canine albumin gave satisfactory results, but the human protein in the form of human stable plasma protein and human albumin were unsuitable for canine kidney preservation. Their experiments suggested that albumin solutions were at least as effective as cryoprecipitate for the 24-hour perfusion of ischaemically damaged canine kidneys.

"Compensatory and Obligatory Renal Growth in Babies and Adults." Sherman J. Silber. (1974, **44**, 421-423.)—The author reports from the Tissue Transplantation Laboratories at the University of Melbourne the effects of transplanting extra kidneys into baby rats and comparing the growth of these kidneys with those of normal litter mate controls. There appeared to be no significant difference in the growth in such transplanted kidneys, nor was there any suppression of normal growth in a baby rat in whom a large adult kidney was likewise transplanted. However, a baby rat kidney transplanted into an adult rat showed some decreased growth. These experiments confirmed the author's hypothesis that normal renal growth does not appear to be reversible and is indeed obligatory in the growing animal.

British Journal of Radiology

By Charles Nicholas

"Urinary Ascites and Obstructive Uropathy." B. J. Cremin. (1975, **48**, 113-117.)—Seven out of 9 babies under 3 months old investigated at the Red Cross Children's Hospital, University of Cape Town, were found to have obstructive uropathy which was responsible for the ascites by perirenal extravasation and resolved in the cases where the obstructive uropathy was overcome successfully. Posterior urethral valves were found in 5 boys, there was one post-circumcision stenosis and 1 girl with ureterocoele obstructing the urinary outflow. 3 illustrative case reports and 5 X-ray pictures are included in the article.

Annales Chirurgiae et Gynaecologiae Finniae

By J. V. Mandel

"Experimental Fat Embolism, Histological Changes in Lungs and Kidneys." V. Makela, A. Alho and R. Lahti. (1974, **63**, 77-81.)—The occurrence of fat embolism in lungs and kidneys, after trauma to the lower extremities, was studied. In the kidneys no distinctive fat deposits in the capillaries, were found. No fibrin collections or thrombi were found in either organs.

"Prognostic Value of Urography in Irradiated Cervical Carcinoma." S. Ruponen, M. Grönroos, A. Mäkinnen and L. Rauramo. (1974, **63**, 127-129.)—126 patients suffering from carcinoma of the cervix had intravenous urographies done, before and after irradiation treatment. Abnormalities were observed in 27 patients, and in 20 of these the changes grew worse, later. Major changes like hydronephroses, hydroureters and non-functioning kidneys were caused by recurrence in 12 out of 14 patients. In 7 patients who had advanced cancer, improvement of the urographic findings was associated with favourable prognosis.

Out of 99 patients in whom no urographic changes were found, 10 patients died, during the follow-up period.

Rozhledy V Chirurgii

By J. V. Mandel

"Mixed Mesenchymal Tumour of the Retroperitoneum." M. Jira, J. Klemenc, E. Mildeova. (1974, **53**, 346-349.)—The authors mention the case of a misdiagnosed retroperitoneal tumour. It proves the difficulties of a correct preoperative diagnosis of this disease.

"Our Experience with Microscopical Diagnosis and Treatment of Chronic Urinary Infections." R. Sanak, T. Antolová, R. Dunová, A. Komadelová, V. Zvara and J. Stojkovič. (1974, **53**, 388-393.)—In conjunction with the evaluation of cultures from urinary specimens from the National Health Institute in Bratislava, the authors point to the ever increasing number of specimens. *B. coli* and *Proteus mirabilis* are met with, most frequently. Patients from the urological University Clinic of Bratislava were investigated, during the first 3 months of 1973. There, a relatively high number of *Proteus* strains with marked resistance to chemotherapeutic drugs, were found.

"Method of Collection of Urine and its Importance for the Reliability of the Bacteriological Findings." A. Utíkalova, H. Hlava and J. Kučera. (1974, **63**, 375-387.)—The authors evaluate the commonly used methods for the collection of urine in 264 adults and older children, and 98 infants. The results of the bacteriological examinations of urine, using different methods of collection, are compared with the method of suprapubic puncture of the urinary bladder which alone is reliable. The authors give an account of their own experience with the suprapubic puncture of the bladder in adults, children, and infants. Their work seems to prove that the commonly used methods of collection of urine bring a high percentage of falsely positive results.

"Sensitivity of Bacteria causing Infections in the Urinary Tract against Antibiotics and Chemotherapeutic Drugs." J. Zahradnický. (1974, **53**, 363-367.)—The author presents information that can be supplied by microbiological laboratories, and may serve as basis for diagnosis and therapy of infections of the urinary tract. He gives an account of the sensitivity of bacteria causing infection of the urinary tract. This information can help the physician in selecting the most effective treatment.

"Chemotherapy of Acute and Chronic Infections of the Urinary System." J. Kučera and H. Hlava. (1974, **53**, 368-374.)—The authors discuss the most important prerequisites of effective chemotherapy, and emphasise the most frequent causes of diagnostic and therapeutic failures. As far as the clinicians are concerned, the most frequent error is urine badly collected for pathological investigation, and erroneous application of the principles of chemotherapy. They deal in detail with the principles of treating the infection. They emphasise the importance not only of disc sensitivity, but also of general and group sensitivity. Finally, they emphasise the importance of antibiotic centres, and summarise the main principles of chemotherapy in chronic urinary infections.

"Chronic Urinary Infections and Stenosis of the Urethra in Girls." E. Hradec, V. Šimon, L. Hradcová and J. Smetanová. (1974, **53**, 399-405.)—The authors stress the importance of urethral stenosis, in chronic urinary infections, in girls. In a group of 220 girls who were examined urologically because of recurring urinary infection urethral stenoses were found in 134. Treatment by internal urethrotomy cured or improved the infection in 88·2%. The onset of the urinary infection occurs mostly between the age of 18 months and 3 years. When reflux is found in girls the urethra ought to be calibrated and what type of reflux is involved must be decided. Only in this way can unnecessary operations be avoided.

"Unusual Clinical and X-ray Pictures of a Urethral Diverticle." J. Scheinar. (1974, **53**, 419-421.)—Unusual clinical and X-ray pictures of a urethral diverticulum are presented, and the difficulties of differential diagnosis pointed out. X-ray and cysto-urethroscopy findings were normal. The diagnosis was based on a shadow on the plain film, and on a palpable resistance in the perineal region. After removal all the symptoms and signs disappeared.

"Growth of Bacteria in Urine of Healthy People, and of Patients with Diseases of the Kidneys and Urinary Tract." J. Buranský, J. Peă, I. Fetisov and E. Franová. (1974, **53**, 394-398.)—The authors studied the curves of growth of *E. coli*, *P. vulgaris*, and *P. aeruginosa*, *in vitro* in the urine of patients, in whom the diagnosis of cystitis, pyelonephritis, glomerulonephritis, diabetes mellitus, was made, and of healthy people. The growth of bacteria was slowest in the urine of patients with glomerulonephritis. Of the bacteria in tested specimens, *P. vulgaris* showed the most intense growth.

"Urological Complications in Diabetes Mellitus." J. Uldrich. (1974, **53**, 406-410.)—The author studied curves of growth of *E. coli*, *P. vulgaris* and *P. aeruginosa in vitro*, from the urine of patients, suffering from cystitis, pyelonephritis, glomerulonephritis, diabetes mellitus, and from healthy subjects. The fastest growth was in the urine of diabetics, and of healthy patients. The growth was slowest from the urine of glomerulonephritics. *P. vulgaris* showed the most intense growth.

"Possible Errors in Diagnosing Ruptures of the Urinary Bladder." V. Drahovský, A. Bauerova, J. Bauer and P. Zelenák. (1974, **53**, 415-418.)—The authors describe three patients suffering from injuries, showing an atypical clinical picture, which caused considerable difficulty in diagnosis. Therefore, they recommend exploratory operation in doubtful cases.

Conferences and Courses

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Further details obtainable from: The Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

Book Reviews

The History of Urology. By L. J. D. MURPHY. Pp. 548, 461 illustrations. Charles C. Thomas. $32.50.

A complete work on the history of urology would fill a good-sized library. This relatively small volume has therefore had to be a brief chronicle of urological ideas and practices through the ages.

The history has been approached from two directions which are presented as parts I and II. Part I, beginning with the beginnings, describes ancient without reference to modern practices. It consists largely of the author's polished translation of Desnos' monograph of 1914 but Dr Murphy has supplemented Desnos' work when there were major omissions.

Part II—entitled "The development of modern urology"—is a collection of backward looks at the origins of a remarkable number of present-day procedures. These are abbreviated rather more than both the reader and author would have liked, but "the economics of publishing demanded that the final draft be reduced by approximately a quarter".

While most busy clinicians will probably have to be content with the rather potted histories in this beautifully printed and illustrated book, those with more time will be able to respond to its numerous stimuli by using some of the many references listed at the end of each chapter.

It is a nice book to have at home for intermittent leisure reading; certainly no urology department library will be complete without a Murphy's *History of Urology*.

W. K. Y.

Writing Scientific Papers in English. By MAEVE O'CONNOR and F. P. WOODFORD. Pp. 108. Amsterdam: Associated Scientific Publishers. DFL 21.00. About US $7.95.

Although the most important deciding factor in the acceptance of a paper for publication is its content of worthwhile new knowledge, the presentation should be attractive to the reader—it should certainly not be repellent to the Editor and his advisers.

This small book—commissioned by E.L.S.E. (European Association of Editors of Biological Periodicals)—gives readable precise advice on preparing, writing, revising, refining and submitting papers to scientific journals in general; almost everything said applies to medical articles.

I was pleased to see repeated emphasis on the theme "the most relevant guide for an author is the latest set of Instructions to Authors issued by the Journal in which he or she hopes to publish", and that these and the Notes for Advisers for the *B.J.U.* are in line with the recommendations in the book.

There are notes on how to react to a rejection letter and, in more optimistic vein, on how to correct proofs.

One of the five appendices is on Expressions to Avoid giving a Usually Preferred alternative.

This book is described as a "core manual" which will have added to it small companion booklets on the special features presented by different disciplines and languages; there are pockets inside the covers to hold these supplements which are now in preparation.

Adherents to the advice in this book are guaranteed a greater success rate in the acceptance of their papers by this *Journal*.

W. K. Y.

Images of the Seminal Tracts. By JACQUES BOREAU. Pp. 318 with 212 illustrations. Basel: Karger, 1974. $60.25.

This is an atlas of radiographs, principally of the seminal vesicles, demonstrated by injection of the exposed vas deferens. The quality of reproduction of the radiographs is excellent but unfortunately the text is not very good.

The text was originally in French and this is printed alongside the translation into English, a format which is very wasteful of space. There are numerous glaring errors of translation and printing which make the English version very difficult to read. For example, in a description of the radiographic technique it states that a view of the whole pelvis should be taken by "withdrawing the ampulla about 40 cm". If this instruction were followed the result would be disastrous unless it is realised that the "ampulla" refers to the X-ray tube and not the ampulla of the vas deferens.

The author has demonstrated the value of seminal vesiculography in the investigation of abnormalities, some rare, which cannot be shown by other radiographic techniques—hypoplasia and tumour of the seminal vesicles. dilatation and cysts of the ejaculatory ducts etc. These good examples are unfortunately diluted by numerous other illustrations which are shown as abnormalities but do not seem to differ significantly from normal. Examples of these are the changes attributed to reactions to arterial, venous and ureteral lesions.

He clearly illustrates his experience with a wide range of abnormalities of the genital tract and claims to have done more than 2,600 examinations without complications. It is a pity that he has not devoted more space to a discussion of the indications for the procedure to help those who are not fully convinced of its value and safety to decide which patients might benefit from the investigation. Nevertheless, anybody wishing to do seminal vesiculography, who is not familiar with the technique of the examination or the radiological appearances of the seminal tract, will find this book useful.

W. S.

Male Accessory Sex Organs, Structure and Function in Mammals. Edited by DAVID BRANDES. Pp. x+527. New York: Academic Press, 1974. £18·95.

Despite much investigation the prostate gland remains a mysterious organ. In 1963 the National Cancer Institute monograph *Biology of the Prostate*, brought together work by investigators from diverse fields. Since then there have been rapid advances and the timely production of this multi-author review will ensure that it too remains a work of reference for many years. In 19 chapters 27 authorities cover the anatomy, endocrinology, biochemistry and pathology of the prostate gland in man and other mammals. Production throughout is of a high standard. Figures are clear and the reproduction of electron micrographs is excellent. Some authors have added notes in proof of recent advances up to 1974, and it is disappointing that this practice has not been universally followed. In a field where the scientific investigator and practising urologist easily become estranged, a happy balance has been reached so that experimental results are seen in relation to human prostatic disease.

The editor, David Brandes, has produced fine chapters on structure, cytochemistry, and hormonal regulation. The electron micrographs are outstanding, but in these times of austerity the margins appear over-generous. Thaddeus Mann provides a chapter on inhibitory effects of malnutrition on prostatic function. Liao and his group review their work on androgen receptors, anti-androgens, and the uptake of androgen by the prostate. The influence of androgen on DNA and RNA synthesis is lucidly covered by Donald Coffey. Lasnitski reviews her own major contribution in the difficult field of prostatic organ culture, while Fraley examines experimental carcinogenesis and concludes that further study of the human prostatic epithelial cells is required. Pathologists will find the chapter by Kirchheim on the fine structure and cytochemistry of human prostatic carcinoma of particular interest. The volume concludes with a section on ageing in the prostate in which Mainwaring and Brandes examine the structure and functional changes of senescence.

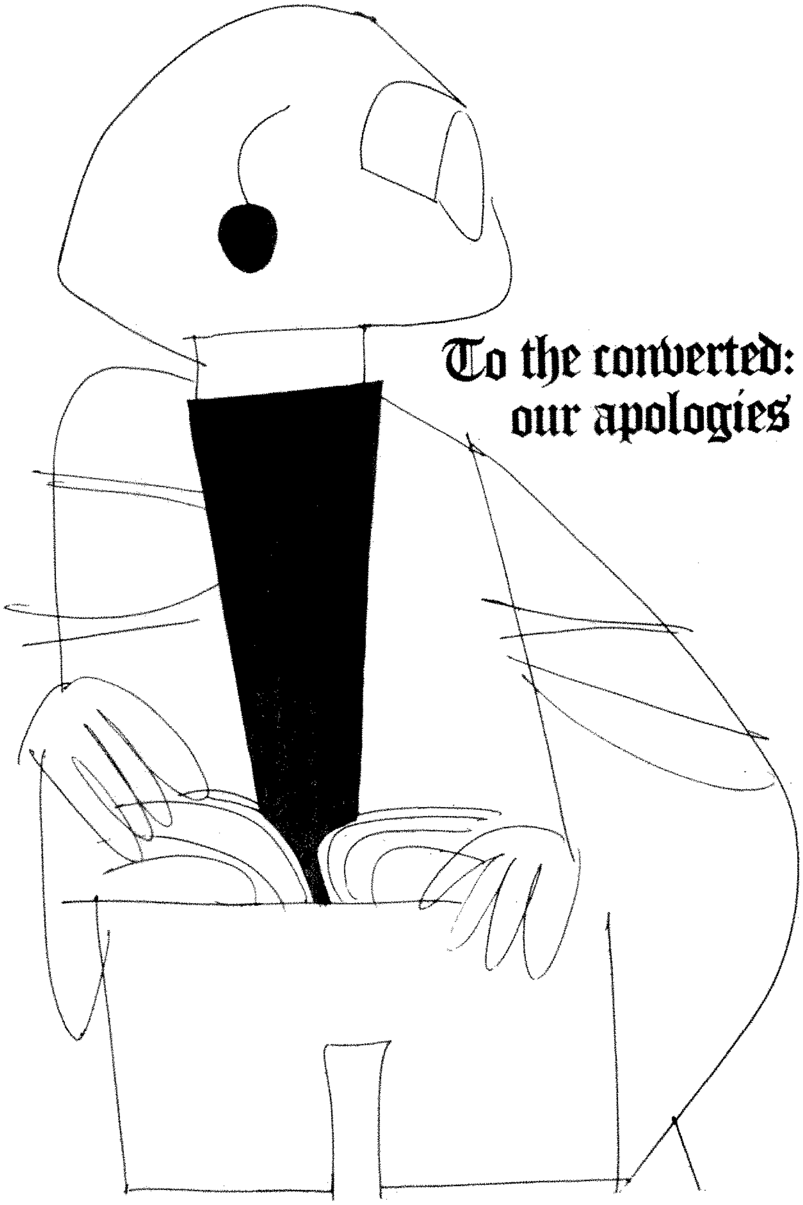
In summary this is an essential book for those engaged in the scientific investigation of prostatic function. Although the emphasis is on animal experimentation there is much to interest the urologist and histopathologist.

A. R. M.

Book Received

Review of Allied Health Education: 1. General Editor: JOSEPH HAMBURG. Lexington: University Press of Kentucky, 1974. $7.50.

Printed in Great Britain by T. & A. CONSTABLE LTD, Edinburgh



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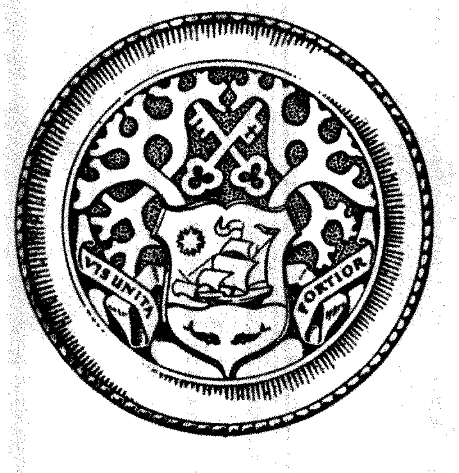

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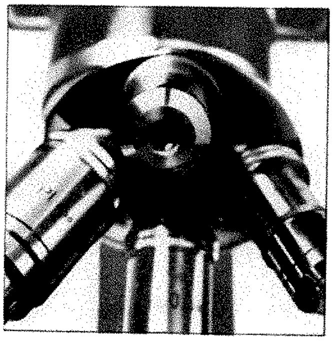

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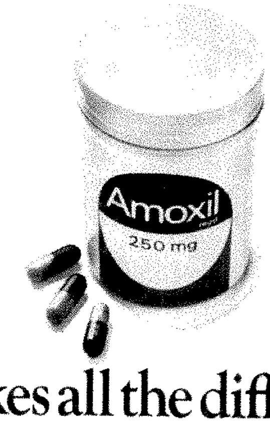

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References
1. 'Antibiotics under the microscope.' A film freely available to the medical profession.
2. Brit. med. J., (1972), 3, 13.
3. Curr. Med. Res. & Opin., (1972), 1, 10.
4. Brit. J. Dis. Chest., (1972), 66, 185.
5. Lancet, (1975), 505.

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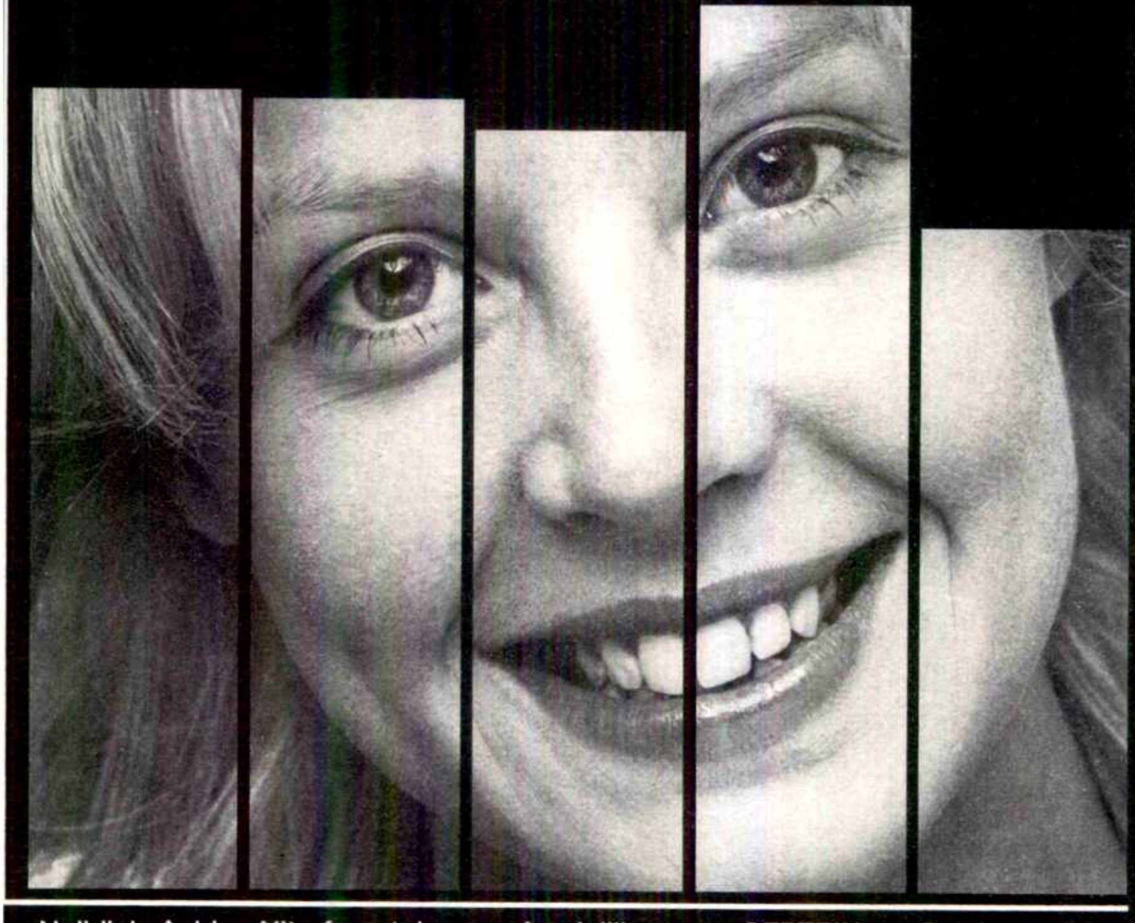

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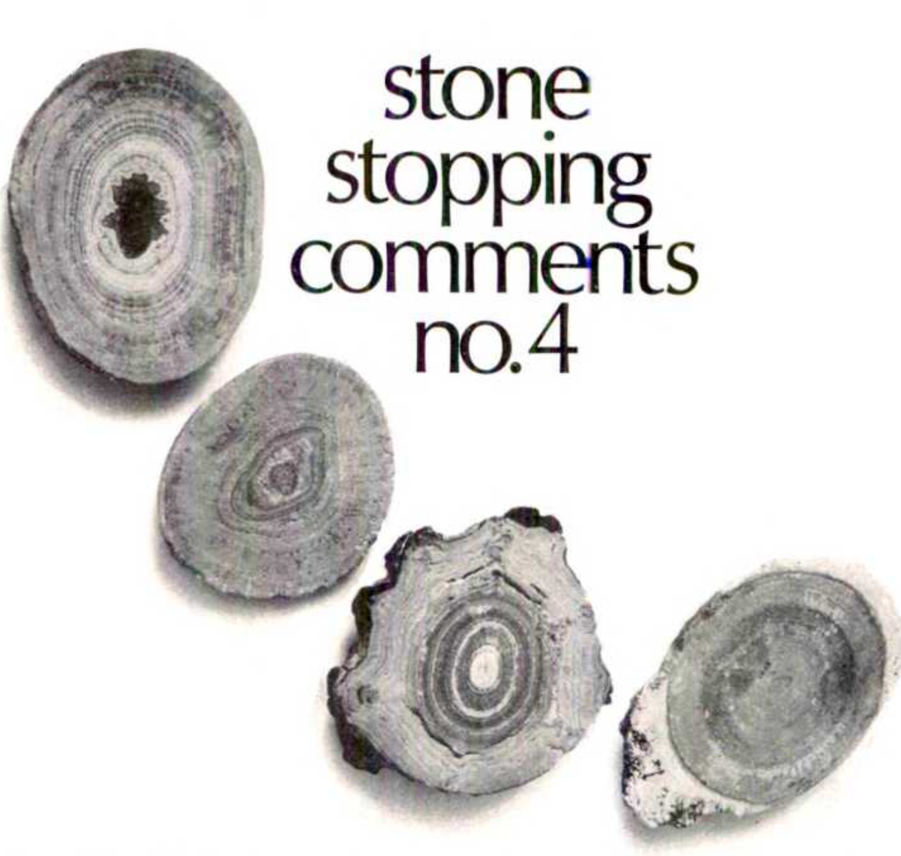

In a recent study[1] measurements of ^{47}calcium and of urinary calcium excretion were made in 125 cases of urolithiasis (78 solitary stone, 47 recurrent).

The authors found that 57 out of 60 patients with hypercalciuria showed raised absorption of ^{47}Ca, whereas 49 out of 106 patients showing similar hyperabsorption of calcium had *normal* calcium excretion. The authors concluded that "... a majority of stone formers, whether they are hypercalciuric or not, absorb calcium excessively from the intestine and this is more prevalent in cases of recurrent urolithiasis."

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1. Brit J Urol, (1974) **46**: 377-384.
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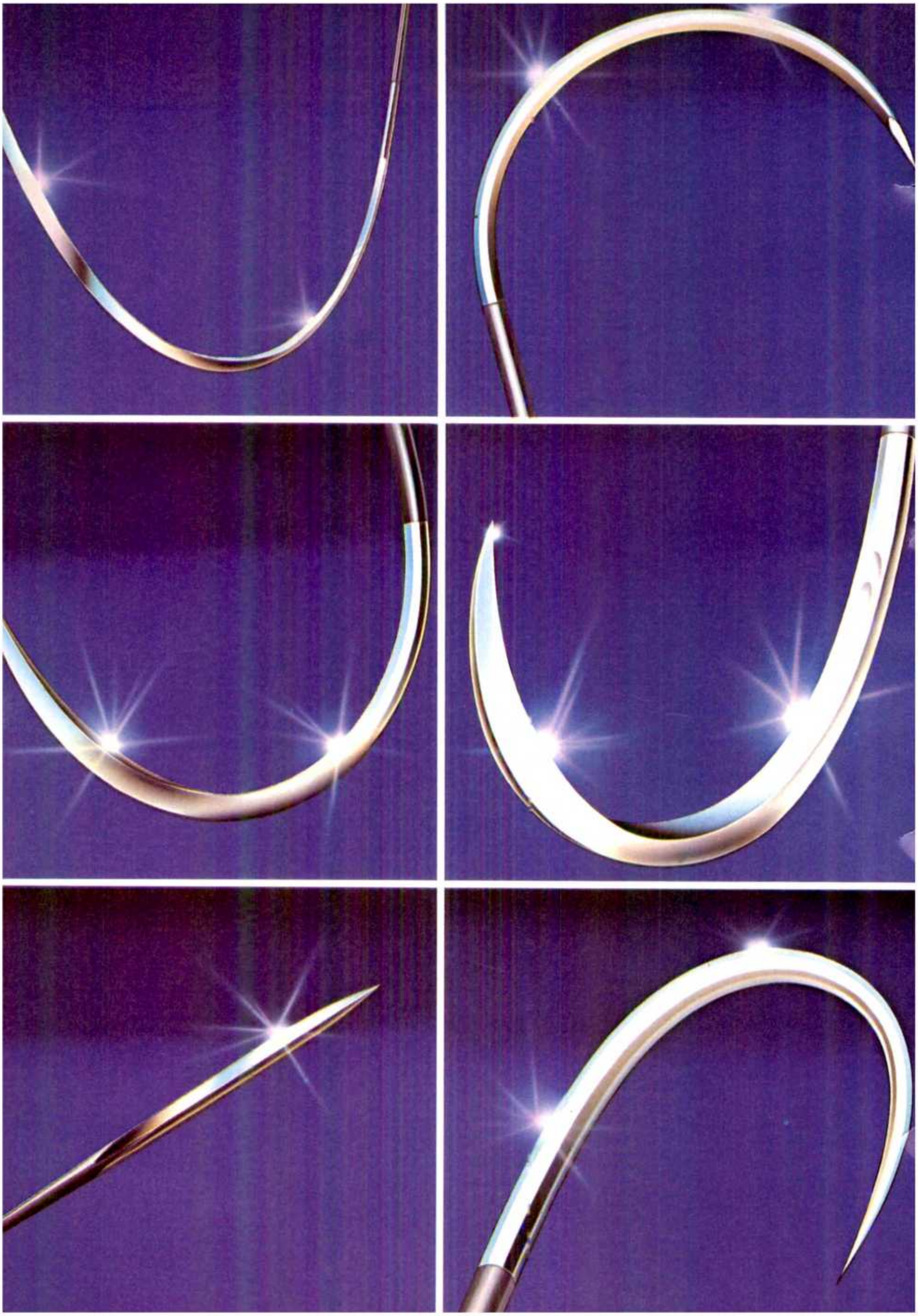

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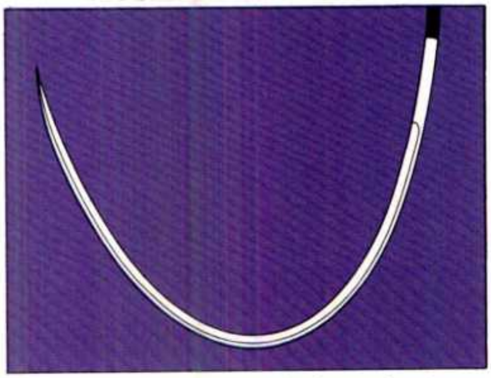

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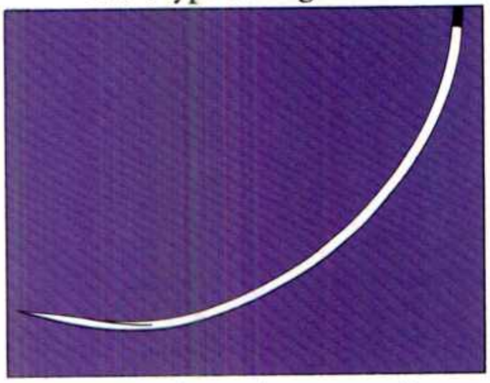

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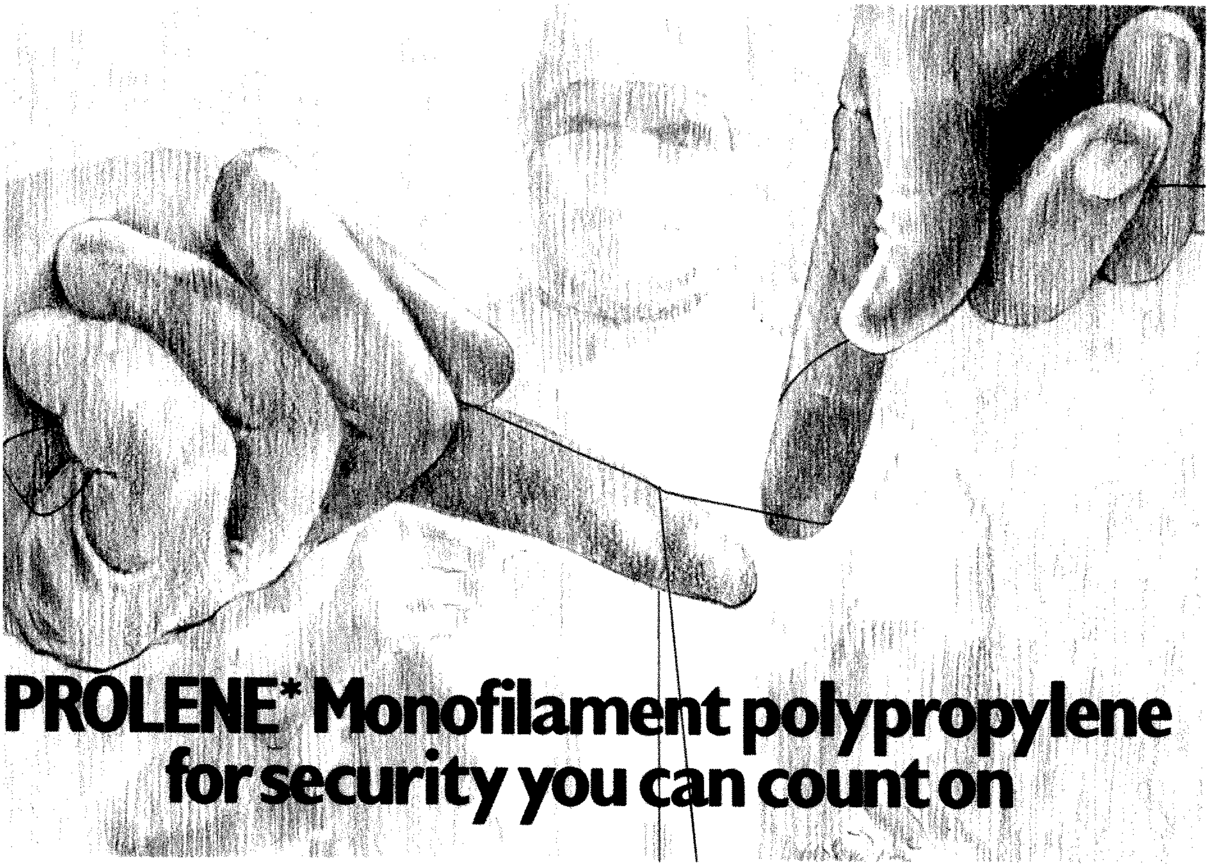
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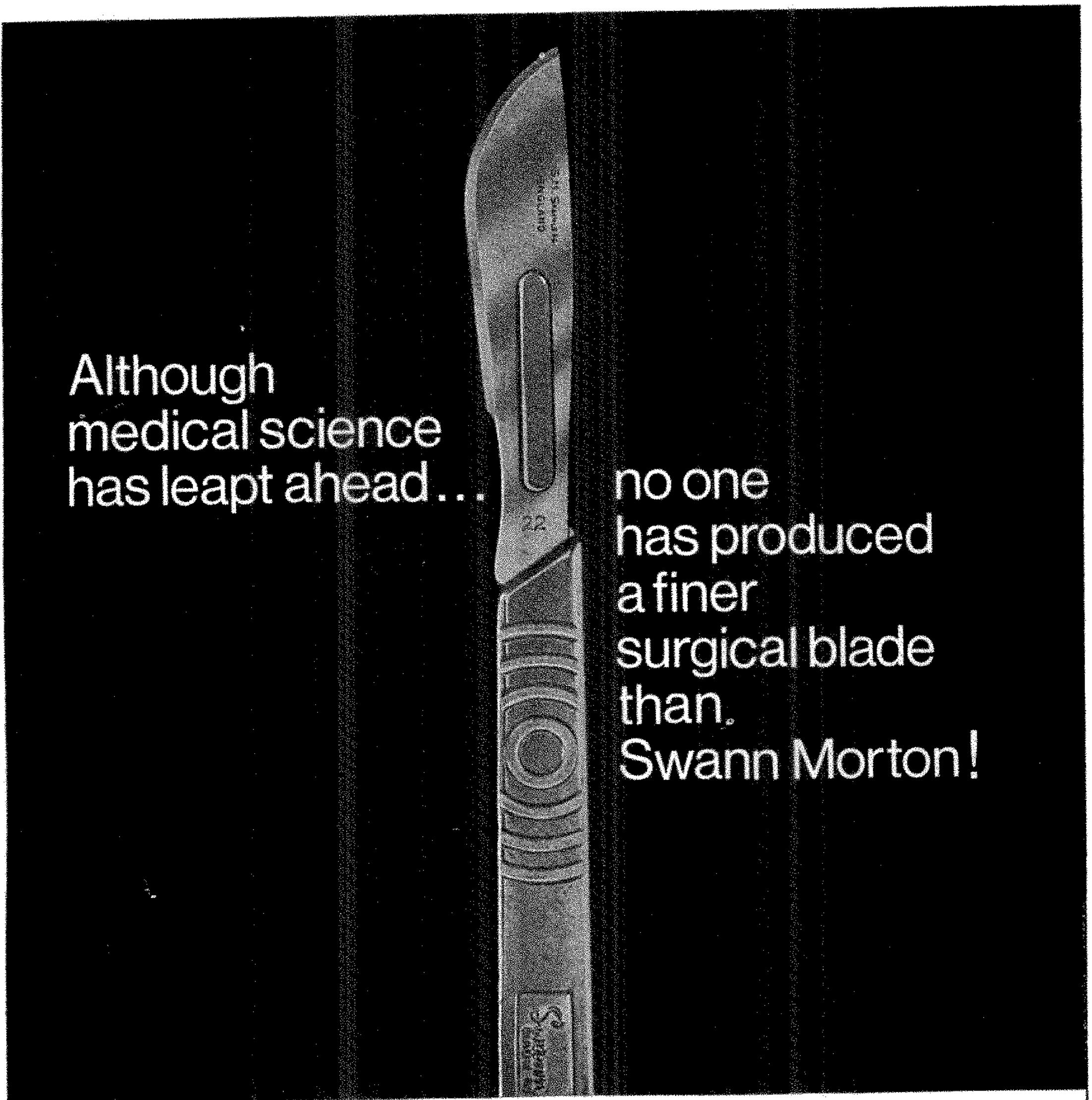

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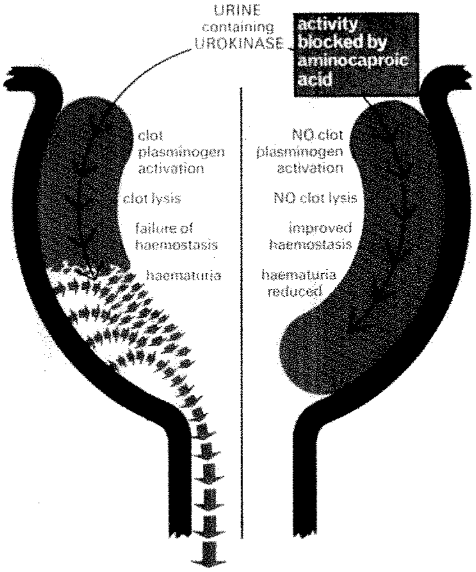

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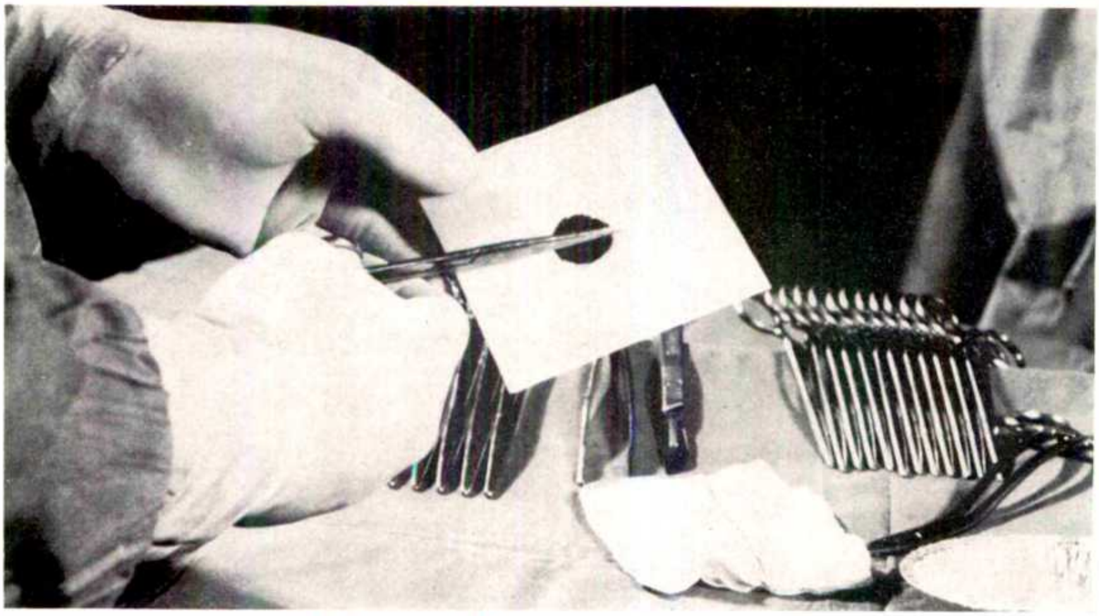

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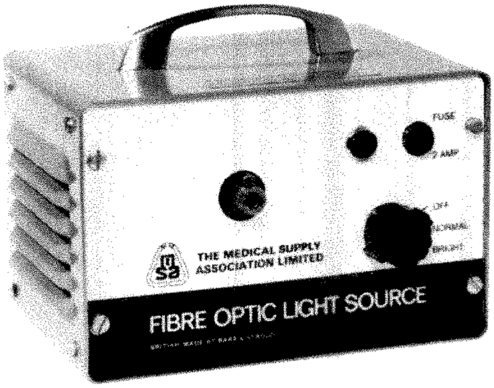

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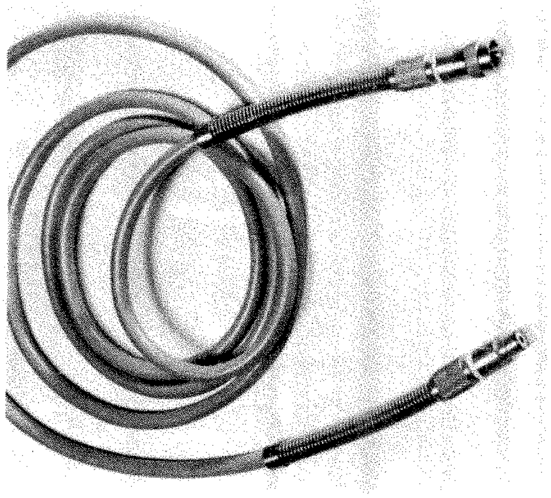

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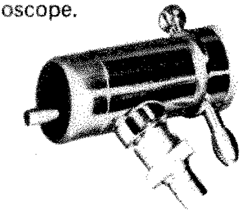

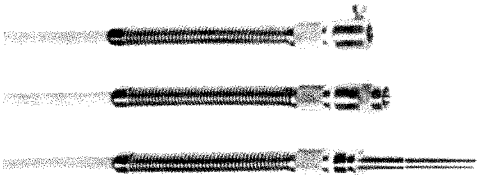

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In Vitro Studies of Subcalyceal Upper Urinary Tract Muscle in Multicalyceal Kidneys

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Although it is generally agreed that nerve fibres are present throughout the muscle layer of the renal pelvis and ureter, there is no such agreement as to the functional relationship between these nerves and the smooth muscle cells themselves. Recent experimental work on isolated preparations of minor calyx from the multicalyceal kidneys of pig and man has demonstrated this muscle to respond in an excitatory manner to α-adrenoceptor and muscarinic receptor stimulation (Longrigg, 1974). In addition the calyx of the pig was shown to possess inhibitory β-adrenoceptors. By means of electrical stimulation studies, evidence was put forward suggestive of an effective innervation of the α-adrenoceptors in both species. This work has now been extended to include the remainder of the upper urinary tract and results presented here are those obtained studying isolated preparations of pelvis and ureter obtained from the pig.

Materials and Methods

Specimens of porcine upper urinary tract were obtained from a local abattoir. Circularly orientated strips of pelvis measuring approximately 1 cm × 3 mm were suspended in a 20 ml jacketed organ bath containing Krebs solution at $38 \pm 0{\cdot}5$°C and well aerated via a glass scinter with a 95% O_2-5% CO_2 mixture. One end of the tissue was firmly anchored to the base of the bath, while the other was attached to a force displacement transducer which in turn gave a permanent tracing of changes in tension on a potentiometric recorder. The ureter was studied in a similar way using 2 cm segments of the organ suspended longitudinally.

Electrical transmural stimulation of similar preparations of renal pelvis was achieved by suspending the tissues between platinum electrodes from which leads were taken and connected to an electrical stimulator capable of supplying square wave pulses of varying frequency, duration and intensity. For transmural stimulation of ureter, the latter was used in the form of longitudinal strips approximately 4 mm wide and 2 cm in length.

Drugs and Krebs Solution

1. *Drugs*

The following drugs were used in this investigation: (—)-phenylephrine hydrochloride (Koch Light); (—)-noradrenaline and (—)-adrenaline as acid tartrate (Koch Light); (DL)-isoprenaline sulphate (Sigma); acetylcholine chloride (Koch Light); atropine sulphate monohydrate (Koch Light); phentolamine mesylate (Ciba); propranolol (I.C.I.); tetrodotoxin (Sigma). A stock solution of 10^{-2} gm/ml was prepared every 2 weeks and stored at 4°C, dilutions for each experiment being made daily as required. Drug concentrations in the text refer to amounts per ml of the salt present in the organ bath fluid.

2. *Krebs Solution*

The following were dissolved and the final volume adjusted to 1 l using distilled water: KCl, 0·35 g; $MgSO_4$, 0·29 g; KH_2PO_4, 0·16 g; $CaCl_2$, 0·37 g; NaCl 6·9 g; NaH CO_3, 2·1 g; glucose 2 g.

Results

1. *Spontaneous Activity and Response to Drugs*

In a series of 49 preparations of pig renal pelvis, 23 exhibited spontaneous changes in tension (after intervals of approximately 10 m) at frequencies of 1 to 12 per min and with amplitudes ranging between 0·4 and 1·4 g. Although

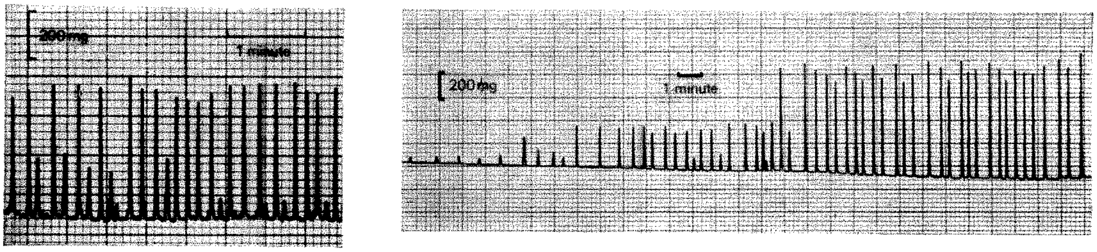


Fig. 1. Spontaneous tension changes recorded from preparations of (*a*) renal pelvis and (*b*) upper third of ureter.

some preparations exhibited fairly regular tension changes the majority were subject to spontaneous variations in both frequency and amplitude (Fig. 1a). The remaining preparations were completely quiescent when observed for periods of up to 1 hour but could be stimulated into rhythmical activity by the addition of noradrenaline (1 μg/ml).

8 out of 10 preparations from the upper third of the ureter developed spontaneous activity within 10 to 15 min. commencing with tension changes in the order of 50 mg and at rates of approximately 1 per min. Over a further period of 10 to 15 min these contractions gradually increased their amplitude and frequency to values around 1 g and 2 to 3 per min respectively (Fig. 1b). The 2 remaining preparations were quiescent when observed over a period of 1 hour but responded to adrenaline (2 μg/ml) with rhythmical tension changes accompanied by a small increase in resting tension. After washing with Krebs solution, these preparations then continued to contract "spontaneously" at rates of 2 to 3 per min and with amplitudes of approximately 1 g.

Preparations from the middle third of the pig ureter responded in a manner similar to that described above. 7 out of 10 studied exhibited spontaneous activity in the form of contractions of 0·8 to 1·5 g amplitude at rates of 2 to 4 per min and similar activity could be initiated in the 3 quiescent specimens by adding adrenaline in a concentration of 2 μg/ml or more.

Lower-third preparations developed spontaneous activity in only 1 out of 10 experiments. This occurred 10 min after setting up the preparation and consisted of 6 solitary contractions over a 4 min period. The remaining 9 preparations showed no spontaneous tension changes when observed for periods of up to 1 hour but again responded to adrenaline in a concentration of 2 μg/ml or more by single bursts of contraction waves together with an increase in resting tension.

Renal pelvis muscle responded to the addition of phenylephrine, noradrenaline and adrenaline by an increase in resting tension and frequency of contraction. Amplitude changes showed a tendency to an initial decrease in this parameter at the higher concentrations. The effects were dose-dependent and logarithmic concentration-effect curves were constructed for each drug utilising changes in tension as the measured response, this parameter being found to give the most reproducible results. Adrenaline and noradrenaline gave equal maximum responses and the effects of these drugs and phenylephrine were expressed as a percentage of this maximum, representative curves for each drug shown in Figure 2a. There was considerable variation in sensitivity of different preparations to noradrenaline and adrenaline and the results of 6 experiments with each drug were pooled in order to plot the graph shown in Figure 2b. Only values between 10% and 90% were included in order that the method of "least squares" may be used to find the best-fitting straight line for each set of points, from which could then be calculated EC$_{50}$ values for adrenaline and noradrenaline (3·0 and 7·59 μg/ml respectively). Even at high concentrations, phenylephrine was capable of eliciting approximately only 65% of the maximum response seen with noradrenaline and adrenaline and possible explanations of this phenomenon are discussed later.

Preparations from upper and middle thirds of the ureter responded to phenylephrine, noradrenaline and adrenaline in concentrations upwards of 4, 4 and 2 μg/ml respectively by an increase in frequency and resting tension, together with a small decrease in amplitude. In response to similar concentrations of the same drugs, lower-third specimens developed single bursts of contractions accompanied by small increases in resting tension, the number of contractions and the increase in resting tension being dose-dependent.

When added to preparations of pelvis or ureter, phentolamine (0·5 μg/ml) was devoid of intrinsic activity. However, after 10 min incubation, this drug was noted to prevent all the previously observed effects of the agonists adrenaline, noradrenaline and phenylephrine. Also it was observed that in the case of renal pelvis muscle, the effects of an approximately EC$_{50}$ dose of adrenaline or noradrenaline could be greatly reduced by as low a concentration of phentolamine as 160 ng/ml.

Isoprenaline (0·031-1·0 μg/ml) was inhibitory when added to spontaneously contracting preparations of pig renal pelvis. It effected a marked decrease in the rate of contraction together with a slight decrease in resting tension and a small increase in amplitude. At 1 μg/ml activity ceased completely (Fig. 3a) but could be brought back to control parameters by thorough washing with Krebs solution. Acting on spontaneously contracting ureter (upper and middle thirds), isoprenaline's inhibitory effects were demonstrated, at a concentration of 0·5 μg/ml, by complete cessation of activity and by the subsequent return of control contractions following washing with Krebs solution. These experiments with renal pelvis and ureter were next repeated after incubating the tissue for 10 min with

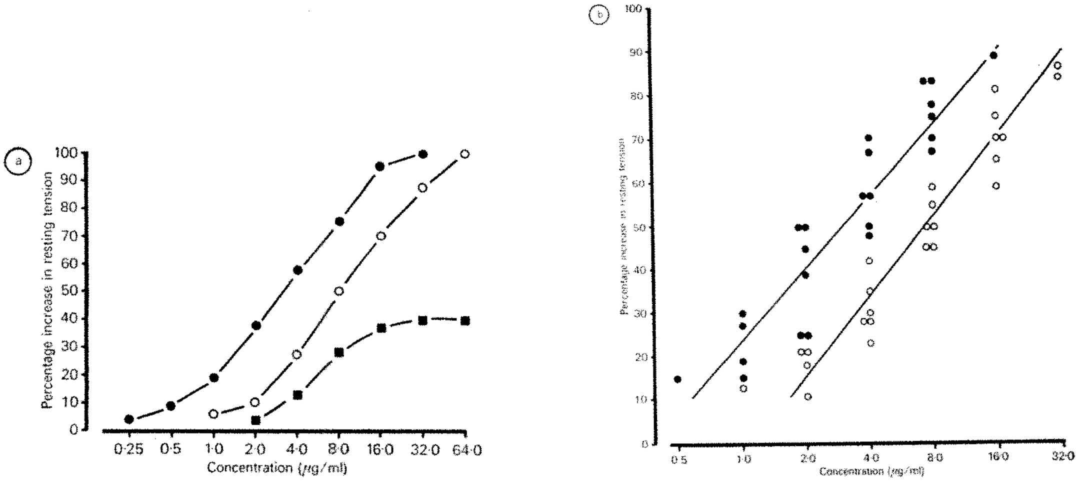


Fig. 2. (*a*) Logarithmic concentration effect curves for adrenaline (●), noradrenaline (○) and phenylephrine (■) on the isolated pig renal pelvis. (*b*) The pooled results of 6 experiments with adrenaline (●) and noradrenaline (○), excluding values above 90% and below 10%.

propranolol in a concentration of 1 μg/ml. Following such treatment it was noted that similar doses of isoprenaline were now completely without effect. Furthermore, after α-adrenoceptor blockade of renal pelvis muscle with phentolamine (1 μg/ml), it was found that a large dose of adrenaline (32 μg/ml) evoked an *inhibitory* response similar qualitatively to that seen with isoprenaline.

Pig renal pelvis responded to acetylecholine (4 to 16 μg/ml) by an increase in both resting tension and frequency of contraction although the maximum increase in resting tension was only approximately 20% of that which could be obtained from the same tissue by the addition of a maximum dose of adrenaline. Responses to the first 3 or 4 additions of acetylcholine were dose-dependent, following which there appeared a gradual decrease in sensitivity of the preparations, even to large doses of the drug. However, if a fixed dose of acetylcholine (8 μg/ml) was repeatedly added to fresh preparations, reproducible increases in resting tension were noted in response to the first 3 or 4 additions. Tissues were therefore subjected to one single application of 8 μg/ml acetylcholine, after which atropine (20 ng/ml) was added to the bath. After 2 min incubation with this drug a similar concentration of acetylcholine was completely without effect and such antagonism with atropine was observed in 5 preparations of pig renal pelvis. Acetylcholine caused stimulatory effects upon all segments of ureter when added in concentrations of 2 to 64 μg/ml, the qualitative responses being similar to those described for noradrenaline, *i.e.* an increase in frequency and resting tension, or initiation of a single group of contractions in the case of lower-third specimens. Pretreatment for 2 min with atropine in a concentration of 20–40 ng/ml was capable of preventing all such responses.

2. *Response to Electrical Transmural Stimulation*

Preparations of renal pelvis and ureter were next subjected to transmural electrical stimulation with varying combinations of frequency, intensity of current, and pulse duration. It was found that by using varying frequencies (up to 100 Hz) and current strength (up to 300 mA), renal pelvis muscle remained completely unaffected by such stimulation until the pulse width was increased to values of around 8 msec or more. At this value and with frequencies greater than 5 Hz, the spontaneously active pelvis muscle responded to a 10-sec train of impulses by extremely variable and inconsistent increases in resting tension. Such responses had no frequency-dependent characteristics, and following treatment of such preparations for 10 min with tetrodotoxin (10^{-7} g/ml) they continued to respond in the same inconsistent manner. Increasing the dose of tetrodotoxin to 10^{-6} g/ml was again found to be without any effect upon the haphazard response to electrical stimulation seen with these tissues. Similar studies were next made before and after treating preparations with phentolamine and atropine in concentrations of up to 50 and 5 μg/ml respectively, yet again no observable decrease in response was noted. If the concentration of either of these drugs was increased to values greater than the above there resulted a gradual decrease in spontaneous activity, rapidly proceeding to a completely inactive preparation.

Not one of the longitudinally cut strips of ureter exhibited spontaneous activity and all were completely unresponsive to electrical stimulation using a pulse duration of less than 4 msec. When increased to values greater than this, then a single stimulus of fixed intensity elicited a single muscle twitch of extremely consistent amplitude. Using such a muscle twitch as the response, the minimum current was found for differing pulse widths such that this response could be produced. In this way a strength duration curve could be constructed from which the chronaxie

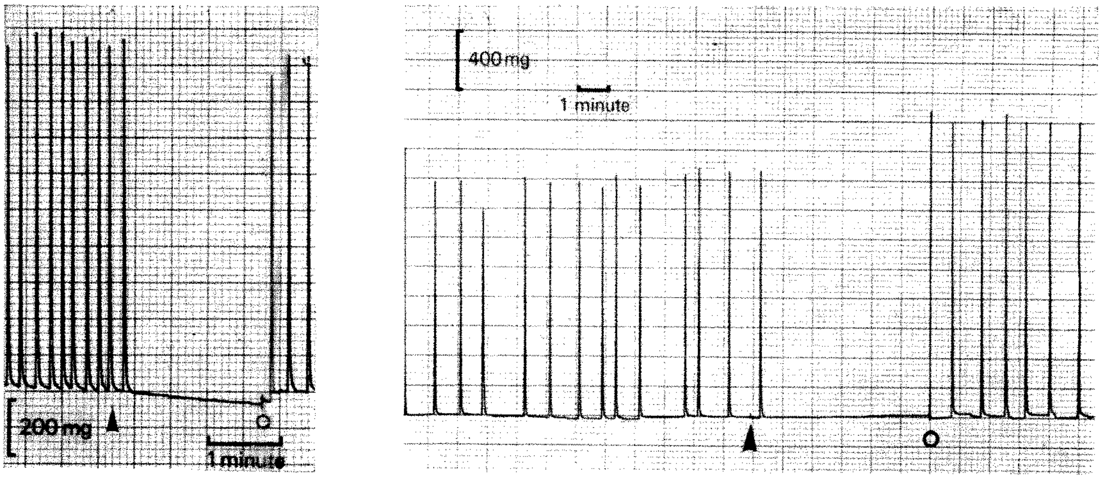


Fig. 3. Effect of isoprenaline (1 μg/ml) on spontaneous activity of (*a*) pig renal pelvis and (*b*) on upper third of ureter. The drug was added at ▲ and the tissue washed with Krebs solution at ○ with return of control contractions.

of pig ureteric muscle was estimated as approximately 7 to 10 msec. Employing supramaximal current, similar preparations were now stimulated with 10-sec trains of pulses, the duration of each pulse being kept constant at 10 msec. With such parameters the tissues responded initially with a muscle twitch similar to that seen when single stimuli were applied. Before the muscle had relaxed completely, however, there occurred a second increase in tension which was of a slower more gradual nature reaching a peak and then decreasing slightly during the 10-sec stimulation period. On cessation of the stimulus there was a more rapid return to baseline tension. In these preparations the magnitude of the initial muscle twitch remained fairly constant and was in the order of approximately 60% to 70% of the subsequent maximum increase in tension.

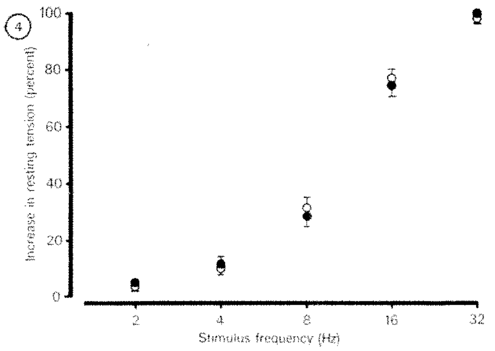
Increases in tension following the initial muscle twitch were frequency-dependent within the range 2 to 32 Hz, and frequency response curves were next constructed for 5 preparations before and after incubation with tetrodotoxin at a concentration of 10^{-6} g/ml (Fig. 4). From these curves it can be seen that tetrodotoxin did not cause any significant decrease in the response to electrical stimulation. It was also observed that the amplitude of the initial muscle twitch was unaltered by this drug. Further studies were next made before and after receptor blockade with phentolamine (50 μg/ml) and atropine (10 μg/ml), and both these antagonists were found to be incapable of lessening the magnitude of either the initial muscle twitch or the subsequent increase in tension of the ureter.

Discussion

A thorough search through the literature has failed to reveal any similar studies of isolated pelvis muscle from animals possessing multicalyceal system kidneys. In contrast, responses of isolated ureteral preparations to certain pharmacological agents have received considerably more attention.

Using an isotonic technique, Macht (1916, 1917, 1918), Roth (1929, 1930) and Satani (1919) noted the pig ureter to respond in an excitatory manner to both adrenaline and physostigmine, and these authors accepted this as pharmacological evidence of both a sympathetic and parasympathetic motor nerve supply to the ureter. More recently Fletcher Deane (1967) demonstrated the inhibitory effect of isoprenaline upon the spontaneously active pig ureter and suggested the presence of β-adrenoceptors in such tissue.

In the present study, the spontaneous activity observed in preparations of renal pelvis muscle differed from that recently observed in a study of minor calyx preparations from the same species (Longrigg, 1974). Whereas calyceal preparations invariably exhibited immediate activity, one had often to wait up to 10 min before spontaneous activity occurred in pelvis muscle, and some preparations remained completely quiescent. When spontaneous activity did occur it also showed a greater variation in rate as can be seen from the histogram in Figure 5. Also, in contrast to the



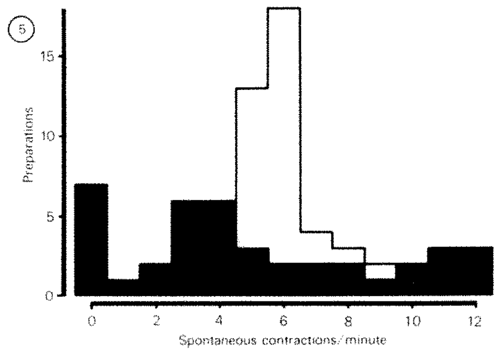


Fig. 4. Frequency response curves for pig ureter before (●) and after (○) treatment with tetrodotoxin. The vertical bars represent the standard error of each mean ($n = 6$). There was no significant difference between the two points at any stimulus frequency (t-test, $P > 0{\cdot}10$).

Fig. 5. Distribution of the rates of spontaneous contraction in a series of 40 fresh preparations each of pig calyx and pelvis. □ = Calyx. ■ = Pelvis.

regular rhythmical changes of tension seen with calyceal preparations, pelvis muscle was often observed suddenly to take on spontaneous variations in resting tension, amplitude and frequency of contraction. These differences were even more evident in preparations of ureter. Although the majority of upper and middle-third preparations demonstrated spontaneous activity, one had to wait periods of up to 30 min for such activity, and it was then necessary to wait a further period of up to 1 hour before the contractions became in any way regular. At this point the rates of such contractions were in the order of 2 to 4 per min, and are similar to those rates quoted by Macht (1916, 1917, 1918). The length of time elapsing before spontaneous activity became regular leads one to question the possibility that such activity reflected a change in the excitability of the smooth muscle cells in response to their new "extracellular" environment. The majority of lower-third specimens remained completely quiescent, and it would thus appear that there is a marked difference in the type of activity observed in preparations of minor calyx, pelvis, upper and lower ureter when observed under almost identical conditions. This aspect will be dealt with in more detail later in relation to the concept of an upper urinary tract pacemaker.

Phenylephrine, noradrenaline and adrenaline were shown to produce dose-dependent excitatory effects upon pig renal pelvis muscle. The inability of phenylephrine to effect a maximum response equal to that of noradrenaline or adrenaline may have been due to this drug behaving as a partial agonist, or perhaps by non-specific effects upon the muscle at the high concentrations used (up to 64 μg/ml). Preparations from all levels of ureter responded to the same drugs in a qualitatively similar manner, although increases in frequency and resting tension were relatively small as compared with pelvis muscle. The concentration-effect curves for these drugs acting on renal pelvis muscle were parallel and showed a potency order of adrenaline > noradrenaline > phenylephrine, in keeping with mediation of the observed effects via α-adrenoceptors (Ahlquist, 1948). Although concentrations are referred to as μg/ml, there is no change in this potency order when such concentrations are converted to the molar form. A similar potency order appeared to exist in most of the ureteral preparations studied, although this could not be quantified owing to the lack of reproducible responses to fixed amounts of the drugs. All the effects of these sympathomimetic agonists could be prevented by prior treatment of the tissues with phentolamine, and it was noted that the effects of an approximately EC_{50} dose of adrenaline could be abolished by as low a concentration as 160 ng/ml phentolamine. The latter signifies a marked specificity of the drug for the receptors upon which it is acting and suggests that the described responses were mediated via interaction with α-adrenoceptors, confirming the findings from studying the potency order of these drugs.

Acting on pig renal pelvis muscle, isoprenaline caused dose-dependent inhibitory effects similar to those seen in calyceal preparations from the same animal (Longrigg, 1974) and capable of prevention by pretreatment of the tissues with the selective β-blocking agent propranolol. Isoprenaline was also shown to have a marked inhibitory effect upon spontaneously contracting segments taken from the upper two-thirds of the ureter. Such an effect could again be abolished by pretreatment with propranolol, and it is suggested that these findings in both renal pelvis and ureter demonstrate the presence of β-adrenoceptors in the muscle of these tissues. Acting on pelvis and ureter, acetylcholine produced effects qualitatively similar to those seen with adrenaline. Their prevention by small doses of atropine (20 ng/ml) indicates a high specificity of this antagonist and is in keeping with the responses having been mediated via muscarinic receptors.

Unfortunately, the presence of autonomic receptor sites in smooth muscle does not, as has often been thought, imply that there must necessarily be a concomitant nerve supply. Having thus shown the presence of receptor sites for both adrenergic and cholinergic neurotransmitter substances, it was next attempted to define by means of electrical stimulation studies whether or not these receptors are innervated.

Preparations of pig renal pelvis were completely unresponsive to stimulation with trains of pulses of duration less than 8 msec, and inconsistent responses were obtained using pulse widths of greater duration. It is believed that the observed responses were due to a mechanism other than nerve depolarisation for the following reasons. First, the threshold pulse width was in excess of the chronaxie value quoted for even the slowest type of nerve fibre (7 msec for frog C-fibres (Bozler, 1938)). Second, although the responses to stimuli of greater duration than 8 msec were inconsistent, it was evident that in some cases the response to a given stimulus after the addition of tetrodotoxin (a potent neurotoxin) was of greater magnitude than that seen prior to the addition of this drug. Third, no decrease in response could be obtained following blockade of either the α-adrenoceptors or the muscarinic receptors with high doses of phentolamine and atropine respectively.

Studies with longitudinal strips of pig ureter revealed this tissue to have a chronaxie in the order of 7 to 10 msec. Although this is less than the values quoted for cat ureter (50 msec—Bozler, 1938), rabbit ureter (180 msec—Bozler, 1938) and guinea-pig ureter (40 to 80 msec—Ichikawa and Ikeda, 1960), it is again in excess of values usually observed for nerve conduction. As the ureter gave such a remarkably reproducible response to a given stimulus, it was possible to quantify the effects of tetrodotoxin by constructing frequency-response curves before and after incubation with this drug. The results showed that there was no significant decrease in response after the addition of tetrodotoxin. Similarly, α-adrenoceptor and muscarinic receptor blockade were both incapable of reducing the magnitude of the ureters' response to this form of stimulus. It is thus felt that the effects of transmural stimulation of ureteral preparations again represented a mechanism other than nerve depolarisation, and were probably caused by direct muscle stimulation. In summary, therefore, these studies of the electrical stimulatory properties of pelvis and ureter are not in keeping with an effective innervation of the receptor sites shown to be present, and provide further differentiating features between these areas and the minor calyx of the same animal, the latter having been shown to have an innervation of its α-adrenoceptors (Longrigg, 1974).

It has been suggested (Gosling and Dixon, 1972) that strong evidence in support of a region acting as a pacemaker site is that of relevant structural specialization confined to that area, and these authors located such an area of atypical smooth muscle cells in the most proximal part of the calyx in the pig. The isolated studies described here also reveal a marked difference between the activity of subcalyceal upper urinary tract muscle as compared with that noted in an earlier study of preparations of calyx. Differences in spontaneous activity have already been discussed. In addition, it has now been shown that although distal upper urinary tract muscle possesses certain receptor sites, these are not effectively innervated as is the case with calyceal muscle. Finally, if the EC_{50} values for adrenaline and noradrenaline are examined and compared with those previously reported for the calyx (Table I) then the greater sensitivity of the more proximal areas becomes evident. There is in fact a gradient of sensitivity of upper urinary tract smooth

Table I

EC_{50} Values (μg/ml) for Adrenaline and Noradrenaline on Preparations of Calyx and Pelvis

Tissue	Calyx	Pelvis
EC_{50} Adrenaline	1·00	3·00
EC_{50} Noradrenaline	2·00	7·59

muscle to the sympathomimetics, the order being calyx > pelvis > ureter. The isolated calyx has thus been shown to possess both physiological and pharmacological properties which distinguish it from the more distal area. If these properties of the calyces in multicalyceal kidneys are considered in conjunction with the structural specialisation referred to earlier, then it would not appear irrational to propose that these observations be interpreted as evidence for a pacemaker system localised to the most proximal part of the upper urinary tract in this species. Whilst many questions remain unanswered, the present study helps to focus attention on an area where future research may further our knowledge of the dynamics of upper urinary tract motor activity.

Summary

Isolated preparations of porcine renal pelvis and ureter were investigated by an isometric technique.

The majority of pelvis muscle preparations exhibited spontaneous activity as did those taken from the upper two-thirds of the ureter, whilst lower-third ureteral specimens remained inactive.

By the use of some autonomic drug agonists and antagonists the presence of α-adrenoceptors and muscarinic receptors was demonstrated at all sites. Evidence of β-adrenoceptor activity was noted in pelvis muscle and also in preparations from the upper two-thirds of the ureter.

Results of electrical stimulation experiments with similar preparations were shown to be against the concept of any effective innervation of these receptor sites.

These findings are compared with earlier studies on the calyx of the same animal, and are discussed in relation to the possibility of the calyx acting as a primary pacemaker site for the upper urinary tract in animals with multicalyceal kidneys.

I am indebted to Mr Thomas Moore for his continued interest and encouragement in this project. In addition I would like to express my sincere thanks to Dr B. Cox, Department of Pharmacology, University of Manchester, for his invaluable assistance throughout the preparation of this paper.

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Conservative Management of Renal Tuberculosis

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Attention has rightly been focused on the importance of obstructive lesions in the renal tract which may be present on diagnosis or develop in the course of treatment of renal tuberculosis (Hanley, 1963; Barrie, Kerr and Gale, 1967; Kerr, Gale and Petersen, 1969).

In 1963 we decided to assess the use of prednisolone as an anti-inflammatory agent in the management of tuberculosis of the renal tract in the hope that medical management specifically directed to the problem of ureteric obstruction, allied to simple techniques of ureteric dilatation where necessary, would obviate the need to remove renal tissue which was unaffected by tuberculosis, and eliminate almost completely the need for more complicated methods of reconstructive surgery, some of which are hazardous. This is an account of our experience of conservative management of renal tuberculosis in 60 unselected patients. The patients have been observed for a minimum period of 5 years and a maximum of 10 years (mean = 7·2 years).

The Patients

During 1963 to 1968, 60 patients suffering from tuberculosis of the kidney were treated in one unit at the City Hospital, Edinburgh.

Age and Sex: Of the 60 patients, 32 were male and 28 female. Only 3 were under 15 years of age and 6 over the age of 55 years. 29 were in the age group 15 to 34 years and 22 between 35 and 54 years. The age range was 10 to 70 years.

Previous History of Tuberculosis: This was present in 9 patients (15%)—4 with previous spinal tuberculosis, 1 of whom also had renal disease, 4 with previous renal disease and 1 who had previous tuberculosis epididymitis. Previous nephrectomy had been carried out in 5 patients, tuberculous disease having developed in the remaining kidney.

Concurrent Tuberculosis: Active pulmonary disease was present in 1 patient, 1 had tuberculosis of a palmar ganglion and 2 (both males) had genital disease.

Investigation: In addition to clinical examination, all patients had a radiograph of the chest, tuberculin test, excretion urogram and, when deemed appropriate, cystoscopy and retrograde pyelography. The latter was carried out in 40 (67%) of the patients. Culture of urine was carried out and sensitivity tests were performed on all positive cultures. As the study developed, renography was added as a routine investigation in any patients showing evidence suggestive of an obstructive lesion, this being performed in 18 patients (30%). There was discordance between the results of renography and retrograde pyelography in 2 patients in respect of the demonstration of an obstructive lesion. Renography suggested an obstructive lesion in 1 patient whereas no obstruction was demonstrated on catheterisation. In the other patient the reverse was demonstrated. All patients had an excretion urogram performed between 4 and 6 weeks after treatment was commenced to determine the progress or development of an obstructive lesion. The frequency of further radiographic examination depended upon the progress of the disease but all had an excretion urogram at the end of treatment.

Bacteriological Status: Tubercle bacilli were isolated from urine in 58 (97%) of patients, smears being positive in 35 (58%). In 2 patients tubercle bacilli were not isolated from urine but were isolated from another site in 1 of them. A bovine strain was isolated from 1 patient. Primary drug resistance was present in 3 (5%) patients (PAS 2, isoniazid 1).

Extent of Disease: 27 patients (45%) showed evidence of involvement of three calyces, hydroureter was present in 29 patients (48%), and evidence of hydronephrosis was present in 16 (27%). The disease was bilateral in 4 patients and an apparently functionless kidney was present in 3. Minor involvement (no definite calyceal abnormality or involvement of only 1 calyx) existed in 17 patients (28%).

Management: All patients received chemotherapy in the form of streptomycin sulphate, sodium para-aminosalicylate (PAS) and isoniazid daily until the results of culture or urine and sensitivity tests were known. The dose of streptomycin sulphate was adjusted for age and, if renal function was impaired, according to serum levels. PAS was given in a dose of 10 to 15 g and isoniazid as 200 mg daily. When initial negative cultures were obtained or sensitivity pattern known, treatment was changed appropriately, usually to a combination of PAS and isoniazid, though latterly 3 patients were treated with supervised intermittent chemotherapy in the form of streptomycin plus isoniazid 14 mg/kg twice weekly. The duration of treatment was planned to be a minimum of 18 months. In fact, 2 patients took only between 6 and 11 months' treatment (both relapsed), 7 had between 12 and 17 months and 51 (85%) over 18 months, 10 (17%) having treatment for over 2 years.

Corticosteroid treatment was given to all patients who had an obstructive lesion demonstrable on diagnosis or on follow-up assessment, with the exception of 1 patient in whom steroid treatment was omitted in error. The plan of treatment was to give 12 weeks' treatment with prednisolone 5 mg 4 times a day, this being based on experience in pulmonary tuberculosis (Horne, 1966). The dose of prednisolone was gradually reduced, usually at a rate of 5 mg monthly. Although a few patients noted weight gain and a little mooning of the face in the initial stages of treatment, no important side-effects of treatment were observed.

Surgical Treatment: It was planned to consider surgical treatment only after the requisite period of 12 weeks of conservative treatment had been given. The management of individual patients was discussed as appropriate and surgical intervention planned accordingly. This aspect is described further in the section recording the results of treatment.

Hospital Treatment: Of the 60 patients, 14 (23%) were managed wholly as out-patients. The longest period of stay in hospital was 32 weeks and the average 7 weeks.

Results of Treatment

In all 60 patients, tubercle bacilli disappeared from urine as shown by repeated negative cultures. Relapse occurred in 2 patients (3·7%) 9 and 36 months after completion of treatment. Both admitted to taking treatment irregularly and both relapsed with resistant organisms (PAS 1, isoniazid 1). 1 relapsed with evidence of hydronephrosis and ureteric obstruction. Both were successfully re-treated.

Table I

Frequency of Ureteric Obstruction in 60 Patients with Renal Tuberculosis.

Ureteric obstruction not demonstrated		30
Ureteric obstruction present		30
Ureteric obstruction present at start of treatment	23	
developed during treatment	6	
developing following relapse	1	
	30	
Treated with prednisolone	29*	
		60

* Prednisolone omitted in one patient in error

Table II

Results of Treatment of 29 Patients with Ureteral Obstruction by Chemotherapy plus Prednisolone

Ureteral obstruction relieved: no surgical treatment necessary		21 (72%)
Ureteral obstruction unrelieved:		8 (28%)
Bouginage	1	
Davis ureterostomy	3	
Diversionary operation	1	
Nephrectomy	1	
Minor degree of residual stricture	2	

Evidence of obstructive lesions indicating the need for corticosteroid therapy was present in 23 patients (38%) at the time of diagnosis and in 6 patients (10%) an obstructive lesion developed during chemotherapy, corticosteroid treatment being added at that stage. 1 patient who relapsed developed an obstructive lesion. Prednisolone treatment was omitted in error in 1 patient. There were thus 29 patients who were treated with prednisolone (Table I). Conservative treatment was successful in relieving the obstructive lesion (Figs. 1 and 2) in 21 of these 29 patients (72%) though it was necessary to repeat the course of prednisolone in 2 patients who suffered a rebound obstruction on withdrawal of steroids on the first occasion. Both patients complained of loin pain at the time of the rebound phenomenon. Of the remaining 8 patients, 3 required intubation (Davis), 1 bouginage, 1 nephrectomy because of a destroyed kidney and 1 a diversionary operation (nephrostomy) of his remaining kidney. In 2 patients, the obstruction was not completely relieved and we now recognise that this was due to a failure to intubate sufficiently early at a time when it was clear that corticosteroids had failed to secure the desired relief of obstruction (Table II).

Nephrectomy was carried out in 4 patients (6·7%), once for persistent secondary bacterial infection in a largely destroyed kidney, once in a patient who had erroneously not been given prednisolone and once in a patient who had recurrent haematuria. However, in this patient histological examination showed the presence of salicylate nephropathy, his tuberculous disease being completely healed. The fourth patient had a rebound hydronephrosis after steroid withdrawal and a

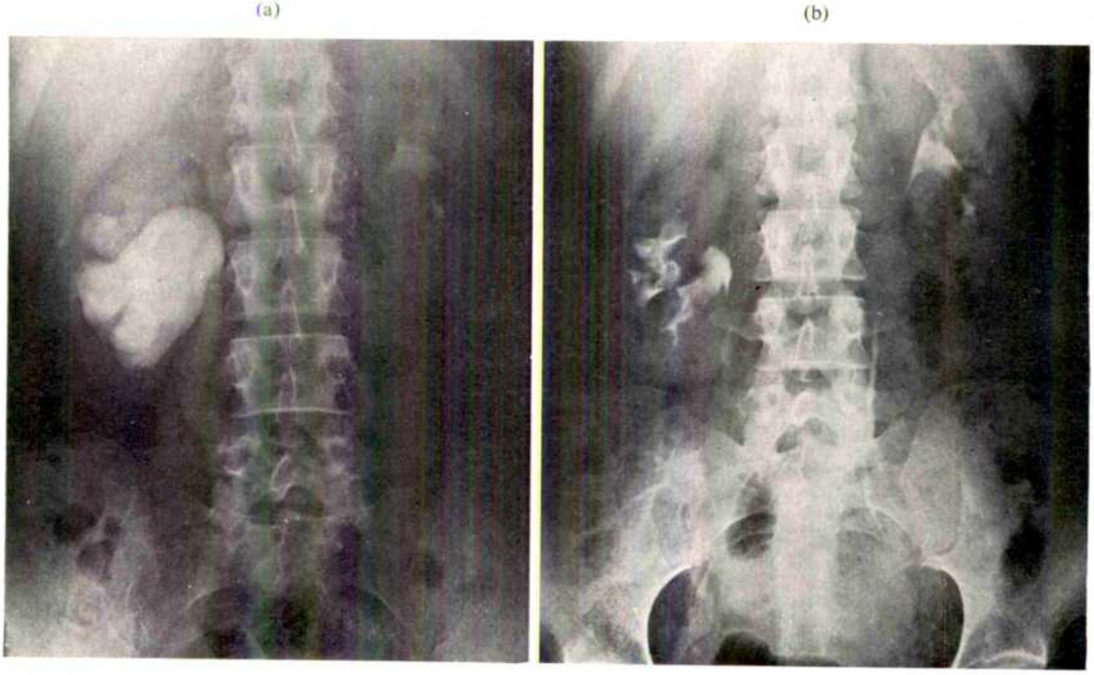

Fig. 1. Excretion urogram (a) before treatment showing grossly dilated ureter and severe hydronephrosis and (b) after treatment with anti-tuberculosis drugs and prednisolone for 12 weeks.

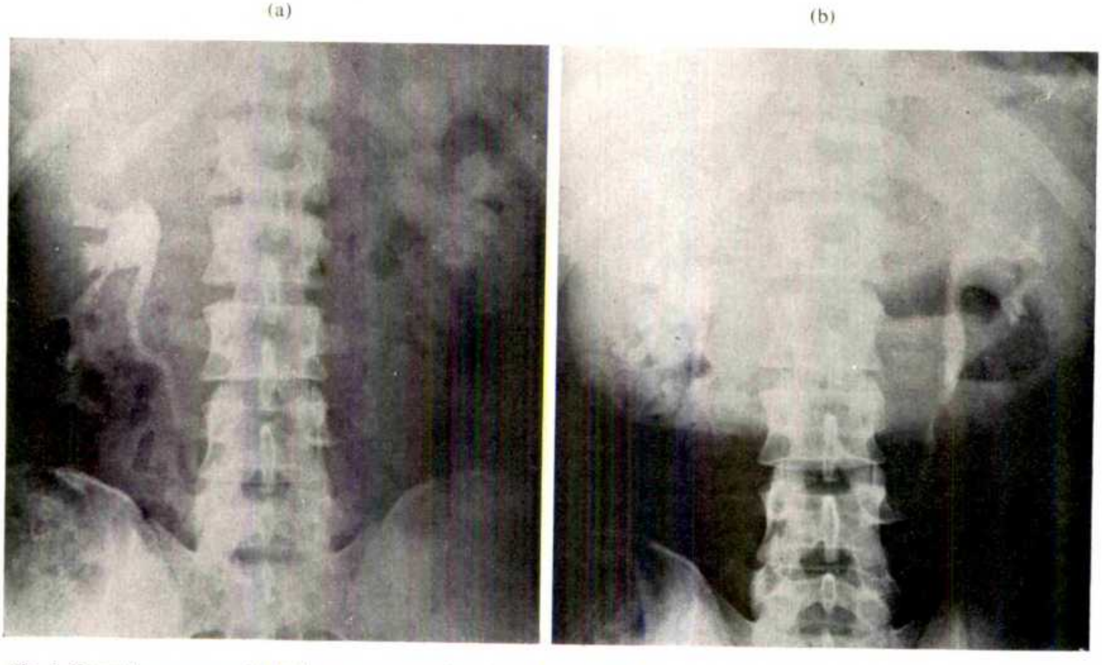

Fig. 2. Excretion urogram (a) before treatment showing grossly dilated ureter and severe hydronephrosis and (b) after treatment with anti-tuberculosis drugs and prednisolone for 12 weeks.

nephrectomy was immediately carried out in another hospital without prior consultation. Thus in only 1 patient was the nephrectomy carried out for what we now regard as proper indications.

No instance of hypertension has been detected. Only 1 patient has experienced persistence of symptoms of recurrent loin pain, frequency and dysuria necessitating nephrectomy. She was cured of her symptoms by operation. 2 other patients have had occasional minor symptoms or urinary tract infection.

Renograms were performed in 18 patients. No repeat examination was carried out in 9 patients. In the other 9 patients, improvement in function was recorded in 7 patients and no change was observed in 2, 1 of whom was the patient with a destroyed kidney and recurrent urinary tract symptoms.

No deaths have occurred from tuberculosis. 2 patients have died, however, 1 from cardiac failure associated with a ventricular septal defect and 1 from injuries sustained in a car accident.

Discussion

We believe that the results achieved demonstrate that the conservative management of renal tuberculosis is wholly justified, that nephrectomy is rarely necessary and that proper treatment by corticosteroids will significantly reduce the need for surgical procedures designed to relieve obstructive lesions of the renal tract.

Lattimer *et al.* (1965) and Radenbach (1968) have already demonstrated the effectiveness of conservative management and that if proper chemotherapy is given, tubercle bacilli disappear from urine in all cases. In our series standard chemotherapy with streptomycin, sodium para-aminosalicylate (PAS) and isoniazid was used in conventional doses with attainment of negative cultures in all patients. Ethambutol and rifampicin may well replace streptomycin and PAS in initial treatment but there is no special merit in the rotating scheme of chemotherapy recommended by Gow (1971). With what used to be considered standard chemotherapy—streptomycin, PAS and isoniazid—a period of 18 months' treatment is recommended if relapse is to be avoided. However, in newer regimes containing rifampicin it may be possible to reduce the period of chemotherapy: this has, however, still to be proved. The relapse rate of 3·7% is similar to that recorded in other series and was due to failure on the part of 2 patients to take treatment properly, a problem which is common to all forms of tuberculosis. Nephrectomy does not obviate the need for chemotherapy as the disease is commonly bilateral (Medlar, 1929). 5 patients in this series, who had previously undergone nephrectomy, developed disease in the remaining kidney. Lattimer *et al.* (1965) state that their policy was to recommend a 6-month period of semi-ambulatory rest, but observed that those who continued activity had done just as well as those who had rested. O'Flynn (1970) has stated that 6 months' sanatorium treatment is necessary but it is our opinion that there is no need for prolonged hospital treatment and that most patients can now be treated wholly as out-patients.

Reference has already been made to the importance of ureteral stricture due to tuberculosis. Our results suggest that corticosteroid therapy is an important therapeutic measure in the management of such obstructive lesions whether they are present at the time of diagnosis or occur in the course of treatment. Opinion regarding the value of steroid therapy in the situation is confused. The opinion has been expressed that "steroids are probably valueless, though this is in dispute" (*British Medical Journal*, 1971). Zeller (1969) recommends that corticosteroid therapy should be given together with chemotherapy in all cases of obstruction of the ureter due to tuberculosis, but Claridge (1970) asserts that the results are sometimes exceptionally good but more often are disappointing. On the other hand, very satisfactory results are reported by Okilačány, Škutil and Payer (1963). In 14 patients suffering from renal tuberculosis complicated by ureteric obstruction, the obstruction rapidly disappeared in 13 (average 51 days) in those treated with prednisolone, and of 10 patients who did not receive prednisolone, in only 6 was the obstruction relieved (average 145 days). Prednisolone was given for a period of 42 days, commencing with 40 mg daily for 10 days, and reducing the daily dose by about 10 mg every week thereafter. Zeller and Rothauge (1972) demonstrated ureteric obstruction in about 37% of 266 patients suffering from renal tuberculosis. Relief of the obstruction was observed in about one-third of patients treated with corticosteroids. In our series, obstruction was relieved in 21 (72%) of the 29 patients treated with prednisolone at a daily dose of 20 mg for a minimum of 10 weeks. Our experience suggests that if relief of obstruction is not attained within 6 weeks by medical management, surgical measures should be employed at this stage, bouginage or Davis ureterostomy often being completely successful. A rebound of obstruction after withdrawal of steroids is amenable to re-treatment. The rebound may be heralded by loin pain. It is agreed that the force of the argument in favour of using corticosteroids would be increased had a controlled trial been carried out. However, we considered such a trial to be unethical, agreeing with Moore and Diaz-Ball (1969) that "one should not sit idly by and observe a kidney being destroyed by hydronephrosis secondary to a tuberculous stricture while successfully treating the primary disease".

The establishment of a base-line for comparison purposes by excretion urogram and isotope renography is important. It is essential to assess the position 4 to 6 weeks after the commencement of treatment to determine whether steroid therapy has been successful or not; or on the other hand whether an obstruction has developed under treatment when it was not present previously. Subsequently, isotope renography at increasing intervals will minimise radiation hazards and excretion urography can be employed at infrequent intervals or when renograms suggest that obstruction to outflow has occurred. As suggested by Gabriel (1971), serial estimation of creatinine clearance may be of assistance in assessing progress and determining management.

Nephrectomy, either total or partial, should now be considered necessary only in exceptional circumstances. Anti-tuberculosis chemotherapy, if properly applied, is so effective that even if the kidney is largely destroyed, nephrectomy is unnecessary (Lattimer *et al.*, 1965). Nephrectomy may, however, be necessary in the unusual occurrence of a perinephric abscess, recurrent non-tuberculous infection in a damaged kidney, or hypertension. It is generally accepted that renal tuberculosis plays a very small part in the aetiology of hypertension. Gow (1970) comments that since 1939 about 46 cases of hypertension in association with unilateral renal tuberculosis have been reported, and of these 31 were cured by nephrectomy. Smith (1956), Kaufman and Goodwin (1965) and Schwartz and Lattimer (1967) concluded that renal tuberculosis is an extremely rare cause of hypertension. It has been suggested that in patients with hypertension considered possibly to be due to tuberculosis of the kidney, measurement of renal vein renin should be carried out before operation is offered (Marks and Poutasse, 1973). Fear has also been expressed that malignancy might develop in severely scarred kidneys and be difficult to recognise by urography. However, in a large series of 270 patients, no instance of malignancy was observed (Bloom, Wechsler and Lattimer, 1970).

Summary

The conservative management of 60 patients suffering from renal tuberculosis is reported. Following chemotherapy, bacteriological conversion to negative was obtained in all patients. 2 patients (3·3%) relapsed due to failure to take adequate treatment.

Evidence of ureteric obstruction was obtained in 30 patients (50%)—23 at the time of diagnosis, 6 during treatment and 1 at the time of relapse. Following corticosteroid treatment relief of obstruction was obtained in 72%.

Nephrectomy was carried out in 4 patients (6·7%) but in only 1 of these was the operation carried out for reasons which we now consider valid.

We wish to acknowledge the help of the Medical Illustration Service of the University of Edinburgh in the preparation of the photographs, and of Miss Joyce Holywell for secretarial assistance.

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Short Case Report

Intraperitoneal Rupture of Pyonephrosis

A 55-year-old man was admitted as an emergency with peritonitis. Plain radiographs of abdomen did not show any abnormality. Laparotomy revealed generalised peritonitis with a large, boggy retroperitoneal swelling situated lateral to the second part of the duodenum leaking pus into the peritoneal cavity. Initially this was thought to be due to a perforated peptic ulcer but the duodenum and pylorus looked normal. On exploration, the cavity extended up to the right paravertebral gutter, measuring approximately 22 × 12 × 10 cm. Peritoneal toilet was carried out and a drain inserted into the abscess cavity.

The primary source of peritonitis did not come to light until the patient formed a sinus after drainage of a local abscess in the abdominal wall. An IVP showed no function on the right side and a sinogram (Fig.) through the drain site then revealed the source to be a hydronephrotic right kidney. Nephrectomy was performed. The patient made an uneventful recovery. Histology showed the renal tissue completely replaced by a thick-walled hydronephrotic sac, with pelvi-ureteric obstruction.

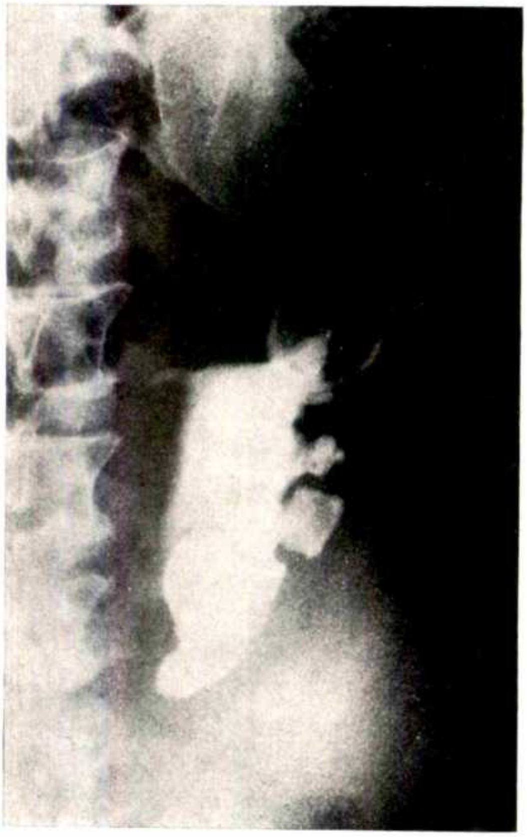

Fig.

Comment

Extraperitoneal rupture of the kidney is relatively common but intraperitoneal rupture leading to peritonitis is rare (Balas, 1971). Rupture is usually associated with a previous abnormality of the kidney, commonly hydronephrosis, as in this case.

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The Immunological Integrity of Matrix Substance A and its Possible Detection and Quantitation in Urine

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Boyce, King and Fielden (1962) described "Matrix Substance A" (Matrix A) as "a component peculiar to renal calculous matrix and calculous patient urine." It was identified as a mucoprotein, immunologically distinct from any component of normal urine, and said to be present in all calcigerous calculi and excreted in the urine of patients with renal calculous disease.

Boyce and King (1963) found a material, immunologically identical with Matrix A in the renal parenchyma of all patients known to have formed calculi. Subsequently Matrix A was also found in the urine of patients with diseases involving renal damage and repair (Keutel and King, 1964).

Patients and Methods

Patients

24-hour urine specimens were collected from 25 patients who were either attending the Stone Clinic or were admitted to the ward with renal colic: 1 : 1,000 phenylmercuric nitrate was added to the 24-hour urine samples as a preservative, as described by King, Boyce, Little and Artom (1958). All the colic patients were shown to have a renal calculus.

Normal Controls

Urines were collected from 20 healthy members of staff with no history of renal disease.

Preparation of Renal Stone Antigen

3 separate antigenic extracts were prepared from batches of renal stones of varied chemical composition. The method of preparation was basically that of Boyce *et al.* (1962). The stones were ground prior to decalcification in EDTA pH 7·7. It was 2 to 4 weeks before decalcification appeared complete. The preparations were then dialysed against running tap-water and freeze-dried.

Separate preparations were made from the following groups of stones:

A. Carbonate stones.
B. Stones with oxalate, calcium, potassium and magnesium.
C. Uric acid stones.
D. High oxalate and calcium stones.
E. High nitrate stones.

Total Non-dialysable Solids from Urine (TNDS)

This substance was prepared as described by Boyce *et al.* (1962).

Antisera to Renal Stone Antigen

Antisera were prepared in New Zealand White rabbits, a total of 8 animals being used. The first rabbits were treated as suggested by Anderson, Lepper and Winzler (1960). The renal stone antigen was suspended in sterile normal saline (20 mg/ml) and 1 ml of this suspension injected at weekly intervals for 5 weeks. Each inoculum was divided into equal portions and given intramuscularly into the animals' forequarters. As the resultant antibody produced only weak precipitin lines when tested by agar diffusion, 2 intravenous doses were subsequently given.

Later, Freunds adjuvant was used with the first 2 doses, followed by a mixture of intravenous and intramuscular doses over a period of 4 months.

The first 4 rabbits received injections from only 1 batch of renal stone antigen, the others were injected with material from all 3 batches of renal stone antigen.

Serological Tests for the Presence and/or Quantitation of Renal Stone Antigen in Urine

1. Immunodiffusion

Ouchterlony's method (1958) of double diffusion in agar was used.

2. Tanned Cell Agglutination Test

It was proposed to treat sheep red blood cells with tannic acid and sensitise them with either renal stone antigen or specific antibody.

It was found that TNDS caused agglutination of sheep red cells and renal stone antigen lysis. Red cells as a passive carrier in a test using either of these reagents was therefore unsuitable.

3. Latex Agglutination Inhibition Test

It was found possible to coat latex particles with renal stone antigen and do a latex agglutination inhibition test for the detection of renal stone antigen. It was necessary to include 0·025% bovine serum albumin as a stabilising agent after the particles had been coated, and in the test diluent.

Dilutions of the material to be tested were made. A constant amount of antibody of known titre was added and allowed to react. Latex particles, coated with renal stone antigen were then added. The agglutination of the latex particles was noted, it being absent where the test material contained sufficient renal stone antigen to react with all the antibody present.

It was possible with this test to detect 25 mg/l of renal stone antigen present in urine. This test appeared to be insufficiently sensitive when compared with other tests used to detect the amount of substance present in patients' urines. Details of this method can be found in Moore (1974).

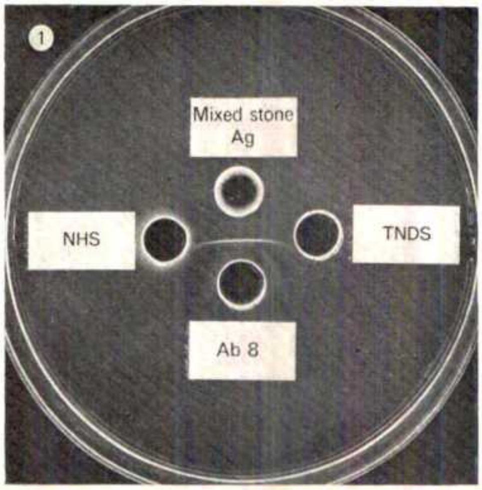
4. Radioimmune Assay

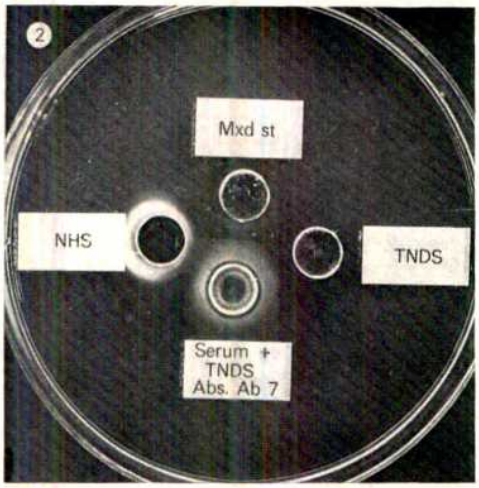
This was derived from the method of Sarsfield and Gowland (1973). Antibody was coupled to cyanogen bromide-activated cellulose. This was added to dilutions of the substance being tested for renal stone antigen. After time had been allowed for the antigen-antibody reaction to take place, any excess antigen was removed by washing the cellulose. Antibody, labelled with ^{125}Iodine was first absorbed with washed cells from human peripheral blood and then added and given time to attach to the antigen-antibody complexes on the cellulose. Free radioactive material was removed by washing and the residual radioactivity measured in a Packard Auto-gamma Spectrophotometer. The radioactivity present, in excess of that present in negative controls, was taken as a measure of the concentration of renal stone antigen present. This method was capable of detecting 2 mg/l renal stone antigen. For details of the method see Moore (1974).

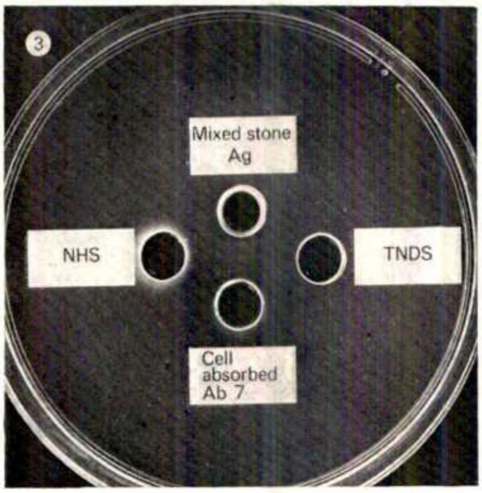
Results

Properties of Antisera prepared against Renal Stone Antigen

All the antisera were tested by double diffusion in agar against TNDS from normal urine, normal human serum, renal stone antigen and extracts of renal stones of differing chemical composition. Antisera were also tested against these reagents after absorption with normal human serum; normal TNDS; normal human serum and normal TNDS; and washed cells from human peripheral blood.







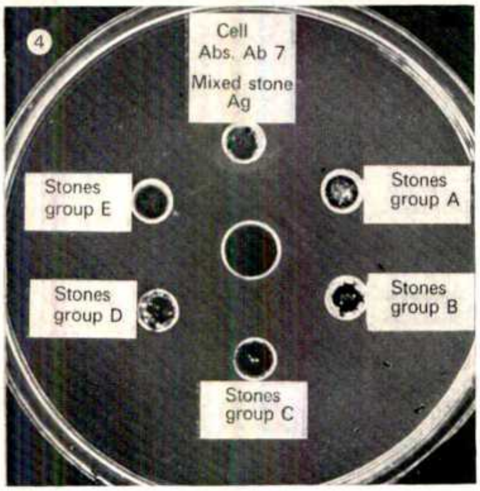


Fig. 1. Antistone serum reacted against TNDS, normal human serum and mixed renal stone antigen.

Fig. 2. Antistone serum absorbed with TNDS and normal human serum, reacted against TNDS, normal human serum and mixed stone antigen.

Fig. 3. Antistone serum, absorbed with human blood cells, reacted against TNDS, normal human serum and mixed stone antigen.

Fig. 4. Antistone serum, absorbed with human blood cells, reacted against extracts of renal stones of differing chemical composition. Types of stones: Group **A**, Carbonate stones; Group **B**, Stones with oxalate, calcium, potassium and magnesium; Group **C**, Uric acid stones; Group **D**, High oxalate and calcium stones; Group **E**, High nitrate stones.

Reactions similar to those obtained by Boyce *et al.* (1962) with their whole antiserum were obtained using the antistone sera produced in this laboratory. These antisera reacted with renal stone antigen, normal human serum and normal TNDS (Fig. 1).

When antigens prepared from various chemical types of renal stones were reacted with the antisera, all preparations gave reactions except the uric acid stones.

However, with absorbed antisera, results did not correspond with those obtained by Boyce *et al.* (1962). These authors claimed that absorption with normal human serum and TNDS left them with a single, strongly reacting antigen-antibody system. In our hands, after such absorption, 3 and sometimes 4 separate antigen-antibody systems were apparent which appeared to be specific for components in the renal stone antigen (Fig. 2). Absorption with washed human blood cells

Table I

Tests for the Presence of Stone Specific Antigens in the Urine or TNDS of Normal Individuals and a Variety of Patients

Category	Immunodiffusion				Radio-immune Assay			
	No. Tested	+	−	% Positive	No. Tested	+	−	% Positive
Normal	20	0	20	0	20	0	20	0
Stone formers	16	11	5	69	12	5	7	42
Stone formers with urinary infection	9	4	5	44	8	4	4	50
All stone formers	25	15	10	60	20	9	11	45

alone produced a similar result (Fig. 3). It can be clearly seen from the figures that the residual systems after absorption are only weakly reactive—some appearing too weakly to show on photographs.

Boyce *et al.* (1962) found that all renal stones, except uric acid or cystine calculi, gave a single precipitin line with their absorbed antiserum. Although the unabsorbed antisera used in the present study reacted with assorted groups of stones, the absorbed antisera only reacted with the mixed stone antigen (which contained stones of many descriptions) and the groups of stones containing carbonate (Fig. 4).

Since the specific precipitin line which Boyce *et al.* (1962) designated Matrix Substance A could not be obtained, the systems detectable with absorbed antisera, and not reactive with TNDS or human serum are henceforth referred to as "stone specific antigens" (SSA) As cell absorption proved to be so easy and efficient, this method was used in any further experiments where absorbed serum was used.

Diffusion Reactions of Cell Absorbed Antisera with Urine

Non-dialysable products from urine were tested at a concentration of 10 × that in the original urine sample.

20 normal control urines were tested in this way. No precipitin lines were seen.

Urines from 25 patients were tested. 10 of the specimens showed no reaction with the antibody. 5 gave 1 precipitin line, 8 gave 2 lines and 2 specimens gave 3 precipitin lines (see also Table I).

Results of Radioimmune Assay (RA)

All the 20 urines from normal individuals with no history of renal infection gave negative results, *i.e.* <2 mg/l.

Of the tests on the urine from 20 proven stone formers, 9 gave positive results, the amount of SSA detected varying from 2·2 to >10 mg/l. 42% of stone formers without urinary infection and 50% with urinary infection were positive (see Table I).

Table II compares the results from 20 stone formers tested by both immunodiffusion and radioimmune assay. It is clear that these 2 tests do not correlate. Since our antisera obviously detect more than 1 stone specific antigen, the most likely explanations would be that:

(*a*) different individuals excrete different stone specific antigens;
(*b*) the 2 tests have different efficiencies with respect to different antigenic systems.

It is also obvious that immunodiffusion will detect antigens which are not detected by radioimmune assay and vice versa.

Table II

Results from 20 Urines from Proven Stone Formers tested by both Immunodiffusion (ID) and Radioimmune Assay (RA) for the Presence of Stone Specific Antigens

Positive by Both Methods	Negative by Both Methods	Positive ID Negative RA	Negative ID Positive RA
5	2	9	4

Table III

Occurrence of Matrix Substance A or Stone Specific Antigens

	% Positive	Detected by
Boyce et al., 1962		
All stone formers	68	Immunodiffusion
Keutel and King, 1964		
All stone formers	28·6	Immunodiffusion
Recurrent stone formers	39·6	
Other conditions	54·5	
All patients examined	36·5	
Present experiments		
All stone formers	60	Immunodiffusion
Recurrent stone formers	65	
All stone formers	45	Radioimmune assay
Recurrent stone fomers	45	
All stone formers	85	Immunodiffusion and radioimmune assay

Despite the non-correlation of the 2 tests (only 5/20 positive by both methods), if both radioimmune assay and immunodiffusion are performed in parallel, 85% (17/20) of stone formers give a positive result showing that they excrete one or more SSAs in their urine.

Discussion

Boyce *et al.* (1962) described their absorbed antiserum as showing 1 single precipitin line when reacted with stone antigen or with urines from stone-forming patients. After absorption, the antisera prepared during this investigation still gave 3 or 4 lines of reaction with the stone antigen and 1 to 3 lines of reaction with urines from stone-forming patients. However, the results obtained using the absorbed antiserum for immunodiffusion do indicate that the antiserum was detecting substances absent in the urine of healthy people but often present in urine from stone-forming patients. We have termed these substances stone specific antigens (SSA).

Radioimmune assay is generally very sensitive and might be expected to detect substances in lower concentration than gel diffusion. When urines were tested for stone specific antigens, the number positive by the immunodiffusion method was greater than the number positive by radioimmune assay. Factors which might contribute to this result might be that the 2 tests are detecting different antigenic systems; that attachment of antibody to cellulose masks too many antigen combining sites; or that the antibody shows a degree of non-avidity in a fluid system to one or more of the antigens (SSA). However this assay will detect SSA in certain urine samples which are negative when tested by immunodiffusion (Table II).

Table III compares the results of Boyce *et al.* (1962), Keutel and King (1964) and the present experiments. It is obvious that the results obtained by different workers using the same technique vary; and that different techniques may not give comparable results.

These facts could probably best be explained on the basis that "*Matrix Substance A*" is not a single antigenic entity or that renal stone antigen (or "*Matrix Substance A*") preparations obtained in different laboratories or from different sources contain a variable number of antigenic components. This would make it uncertain as to whether different techniques would detect the same antigen and also raises the possibility that not all the antigenic components need be excreted by any 1 patient or at any one time by the same patient.

However, despite the fact that several different SSAs obviously exist, using a combination of radio-immune assay and immunodiffusion we have been able to detect some form of SSA in the urine of 85% of renal stone formers, but *not* in the urine of healthy individuals.

Summary

There would seem to be no doubt that most stone-forming patients at some time during the course of their disorder excrete substances not present in normal urine. However, considerable doubt must now exist that "*Matrix Substance A*" is a single antigenic entity or that its presence is confined to the active formation of renal calculi.

We wish to thank Dr C. K. Anderson, Consultant Renal Pathologist, for bringing Matrix A to our attention and Mr R. E. D. Williams, Consultant Urologist, for arranging specimens from patients. We are indebted to the staff of the M.R.C. Mineral Metabolism Unit, University of Leeds and Mr Bryden of St Paul's Hospital, London, for supplying specimens of renal stones.

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The Diagnosis of Renal Pseudotumours

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The term renal pseudotumour was used by King, Friedenberg and Tena (1968) to draw attention to those conditions in which the urographic appearances are similar to those produced by a renal tumour. A common variety of renal pseudotumour is that seen in a kidney scarred and deformed by chronic pyelonephritis or infarction (Felson and Moskwitz, 1969). In these cases surviving normal renal tissue may produce a localised thickening of renal substance giving the appearance of a space-occupying lesion. However, the true nature of such cases is usually evident on urography.

More difficulty is experienced in those cases where the appearance simulating a renal tumour is produced by an infolding of normal renal cortical tissue towards the renal sinus. On the urogram the infolded tissue presents as a localised mass displacing adjacent calyces. Many reports have appeared in recent radiological journals (King *et al.*, 1968; Felson and Moskwitz, 1969; Hartmann and Hodson, 1969; Kyaw, 1972). However the condition has been given scarcely any publicity outside the radiological literature. Our experience indicates that needless nephrectomy is still carried out when pseudotumour is mistaken for malignant tumour. Nevertheless, renal pseudotumour can be diagnosed with confidence without recourse to surgical exploration of the kidney.

Patients and Methods

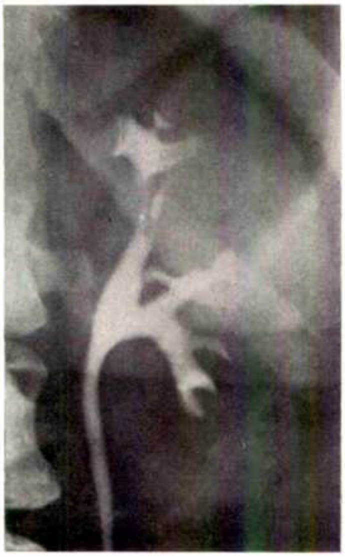
13 patients were studied. 8 presented with abdominal pain thought to be of renal origin and 5 with haematuria. Ages ranged from 27 to 68 with an average age of 52. There were 6 females and 7 males. 11 patients were seen at this hospital. The first of these was subjected to nephrectomy in 1967 when the true nature of the lesion was not recognised. In the remaining 10 patients a confident diagnosis of renal pseudotumour has been made. All these patients were investigated by intravenous urography, nephrotomography and selective renal angiography. Details of the findings will be presented together with details of 2 patients sent to us from other hospitals. Both of these had been subjected to nephrectomy and found to have pseudotumours.

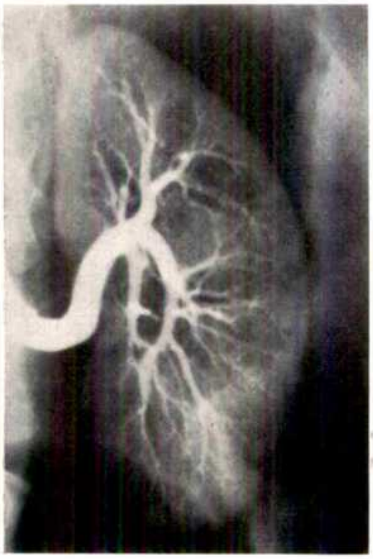
Radio-isotope kidney scans were done on 4 patients. Each patient had a scan 3 hours after injection of 100 μCi of 197 Hg chlormerodrin and immediately after injection of 2 μCi of 99 m Tc diethylenetriaminepentaacetic acid (DTPA) Posterior scans were done with both the gamma camera and the rectilinear scanner.

Radiographic Appearances

At urography a pseudotumour shows as a space-occupying lesion generally situated between the middle and upper thirds of the kidney (Fig. 1). Calyces are usually displaced. At nephrotomography a localised increase in density of the nephrogram may be seen in association with the pseudotumour.

In all our cases the pseudotumour was in the middle or upper third of the kidney. 1 patient had bilateral pseudotumours. In 4 patients the lesion was on the right side and in 8 it was on the left. In 5 cases there was partial duplication of the renal pelvis but in no case was there full duplication of the renal pelvis or ureter.





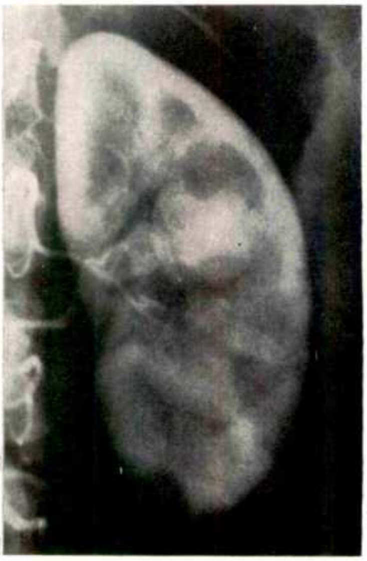


Fig. 1. Intravenous urogram showing partial duplication of the pelvis and a space-occupying lesion between the middle and upper thirds of the kidney.

Fig. 2. Selective renal angiogram (arterial phase). Interlobar arteries displaced by the pseudotumour. No pathological circulation.

Fig. 3. Selective renal angiogram (nephrogram phase). Dense clearly defined pseudotumour nephrogram simultaneous with renal cortical nephrogram.

At angiography 1 patient was found to have 3 arteries each arising separately from the aorta to supply the involved kidney. All other patients had a single renal artery supplying the involved kidney. In each case there was displacement of the interlobar arteries around the pseudotumour in much the same way as they are displaced around a cyst (Fig. 2). No abnormal circulation was shown. All the pseudotumours had clearly defined nephrograms slightly denser than the cortical nephrogram and simultaneous with it (Fig. 3).

Scintiscan Appearances

The 4 cases showed radio-isotope activity at the site of the pseudotumour. In only 2 cases was this activity greater than the activity of the kidney generally (Fig. 4). Chlormerodrin gave more detailed and convincing scans than DTPA. In some cases rectilinear scans with DTPA were misleading but gamma camera scans done immediately after injection of DTPA correlated well with the chlormerodrin scans.

Morbid Anatomy

The reports on the 3 nephrectomy specimens all stated that the pseudotumours consisted of prominent renal columns composed of histologically normal renal cortical tissue. There was no evidence of neoplasm either benign or malignant.

Discussion

The importance of duplication of the renal pelvis in alerting suspicion to the possibility of pseudotumour should be stressed. Nation (1944) found 109 cases of duplication in 16,000 autopsies, an

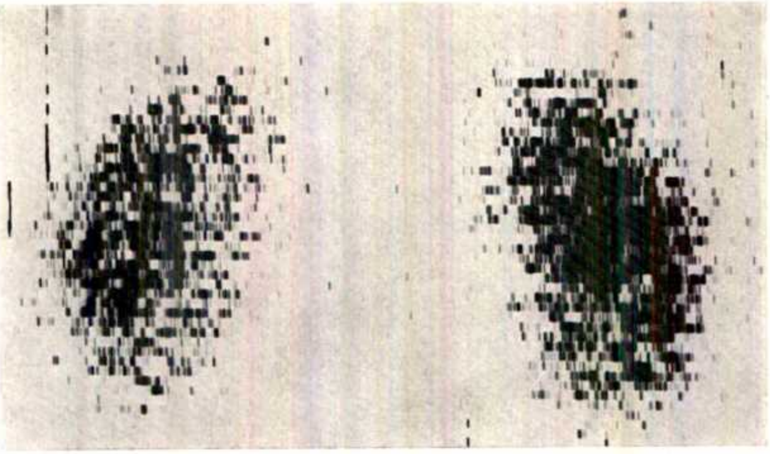


Fig. 4. Rectilinear scan (197 Hg chlormerodrin) showing increased uptake of isotope at the site of the pseudotumour in the left kidney.

incidence of 0·7%. Hartmann and Hodson (1969) found that in patients coming to urography the incidence of complete duplication of the renal pelvis was 4·2% and the incidence of partial duplication 10%. The incidence of partial duplication in our series is 5 out of 13 or 38%, an incidence clearly greater than in the population at large.

Green *et al.* (1972) state that the diagnosis of pseudotumour can be made at nephrotomography on the basis of the increased nephrographic density of the pseudotumour. We have found nephrotomography helpful but we are still not prepared to exclude a neoplasm without angiography.

The most important feature at angiography is that pseudotumours show no pathological vessels, no pooling of contrast medium and no early venous filling. All these are features of carcinoma and carcinoma should not be diagnosed unless at least one of them is present.

The nephrogram of pseudotumour differs from the blush sometimes found in carcinoma in that it has clearly defined margins and is accurately simultaneous with the cortical nephrogram. Cysts present no problem of differentiation because they have no nephrogram.

It has been shown that pseudotumours exhibit uptake of isotope because they consist of normal renal cortical tissue (Felson and Moskwitz, 1969; Green *et al.*, 1972). Braunstein *et al.* (1972) state that pseudotumours show increased radio-isotope activity but we have been able to confirm this finding in only 2 of the 4 cases we have scanned. The important point is that pseudotumours show radio-isotope uptake no matter whether it is equal to or greater than that of the surrounding kidney. There is ample evidence that carcinomas and cysts show clearly diminished radio-isotope uptake (Wagner 1968). Pseudotumours will be diagnosed and needless nephrectomies will be avoided if there is an index of suspicion for the condition. Radio-isotope scanning can certainly help in the diagnosis of a difficult case but until there is more evidence of its reliability it is unwise to spare patients the discomfort and possible hazard of angiography.

Summary

The radiological features of 13 cases of renal pseudotumour due to infolding of the columns of Bertin are presented. 5 of these patients (38%) had partial duplication of the renal pelvis. Pseudotumours show as space-occupying lesions at urography. At angiography they show a clearly defined nephrogram but no abnormal vessels, no pooling of contrast medium and no early venous filling.

Radio-isotope scans on 4 cases of pseudotumour showed uptake at the site of the pseudotumour in contrast to cysts and carcinomas which are known to show diminished uptake.

We wish to thank Dr David Edwards, Director of the Department of Radiology, U.C.H., for his help and advice.

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Hypernephroma with Polycythaemia: a Postoperative Complication

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Hypernephroma has a diverse presentation (Chisholm, 1974). This case shows 2 features and emphasises an operative complication relevant to 1.

History

Mr E. C., aged 73 years, was first seen in December 1973 with increasing prostatic symptoms and a left-sided scrotal swelling. There was a 2-year history of deteriorating urinary stream, frequency, nocturia and hesitancy. During the last 3 years he had noticed a slowly increasing swelling in the left scrotum. He was also aware that recently his skin had become darker and his lips and face a deep bluish colour.

Examination

This showed a plethoric, 14-stone man with cyanosis of his mucous membranes (B.P. 170/100). The other relevant feature was a large left-sided varicocele. The spleen, liver and kidneys were not palpable. The prostate gland was small and benign.

Investigations

A full blood-count showed a haemoglobin of 20·8 g, PCV 62·3%, white blood count 9,000/cu mm and platelets 260,000. The blood volume was 100·9 cc/kg (normal 65 to 85 cc/kg), red cell mass 64·5 cc/kg (normal 28 to 35 cc/kg) and plasma volume 36·4 cc/kg (normal 40 to 50 cc/kg). The serum iron was 47 μg% and sternal bone marrow examination showed generalised marrow hyperplasia with a slight erythroid preponderance. An intravenous pyelogram showed a 12 cm mass in the lower pole of the left kidney and a renal arteriogram confirmed this to be a carcinoma. The chest X-ray was normal.

Management

Preoperative treatment was aimed at reducing the red cell mass and blood volume by repeated venepuncture. 12 units of blood were removed (one at a time) over 17 days, resulting in a haemoglobin of 13·9 g and a PCV of 45%. BP at the end of the course was 115/90. The fall in blood pressure was maintained during the first three venepunctures but thereafter tended to recover prior to the next venepuncture.

The venepunctures were carried out slowly and the systolic blood pressure fell by an average of 15 mm Hg during the procedure. 3 days after the last venepuncture a radical nephrectomy was performed and histology confirmed an adenocarcinoma of average grade. At operation, in spite of minimal blood loss, it was difficult to maintain the patient's blood pressure, the systolic level was recorded at 60 mm Hg for approximately 90 minutes.

The following day the patient had not passed urine and catheterisation obtained only 150 cc. Large doses of diuretics were administered; these failed to produce a diuresis and treatment for acute renal failure was instituted. The proposed aetiology was acute tubular necrosis in the remaining kidney secondary to the hypotensive period at operation.

The patient was treated with fluid restriction and did not require dialysis. Renal function returned by the 10th postoperative day and thereafter he made good progress.

When seen 2 months later he remained well; his haemoglobin was II g, blood urea 95 mg%, potassium 5·0 mEq/l and bicarbonate 20 mEq/l.

Discussion

A third of patients with polycythaemia have haematological complications of thrombo-embolism and haemorrhage in varying severity. These have been ascribed to the hypervolaemia and increased red cell mass, with resultant sluggish blood flow and capillary distention. There is also a complex haemostatic defect manifested by ineffective clot formation despite the presence of normal or increased cellular and plasma coagulation factors. Surgery in these patients carries a high morbidity and mortality, which has been recorded by many authors (Fitts *et al.*, 1960, Rigby *et al.*, 1960).

Wasserman and Gilbert (1963) analysed large series to determine the outcome of major surgery; 5 patients had a renal lesion. The patients' polycythaemia was controlled preoperatively by repeated venepuncture. The observed complication rate of the series was 45%, with an 18% mortality rate. In relation to the preoperative haematological control, 83% of the uncontrolled group had complications and 21% of the controlled group. The duration of the normal preoperative haemoglobin was found to be important as there is a complication rate 5 times greater with a short or immediate period of control than with a long control period.

In the patient presented in this paper, there were no apparent thrombotic or haemorrhagic complications but the hypotension during surgery can be explained as an outcome of the polycythaemia and short preoperative control period. In polycythaemia there is vascular weakness and capillary overdistention as a direct result of the increased blood volume (Fitts *et al.*, 1960). Repeated venepuncture to reduce the red cell mass in the presence of vessel overdistention reduces the vascular tone. With this reduced vascular tone there is peripheral pooling of the circulating volume during surgery and thus reduced venous return and hypotension. It is probable that with prolonged preoperative control of the polycythaemia the vascular tone would have returned to normal and this complication might not have been encountered.

Summary

A case of acute renal failure following radical nephrectomy for hypernephroma in a 72-year-old man is presented. It is postulated that this was a direct result of vascular weakness from preoperation treatment of the overdistended vessels by repeated venepuncture over too short a period, with resultant loss of vascular tone.

I would like to thank Mr P. R. Riddle for his permission to report this case and his help in preparing the text.

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Short-term Cadaver Kidney Preservation

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Over the last 2 or 3 years several perfusion machines have become available for long-term preservation of cadaver kidneys (Belzer and Kountz, 1970; Claes and Blohme, 1970; Belzer *et al.*, 1972; Claes, Aurell and Blohme, 1972; Johnson, 1972; Johnson *et al.*, 1972; Snell, 1972; Williams and Gordon, 1972; Callum, Bewick and Battye, 1973; Claes and Blohme, 1973; Hendry and Stevenson, 1973; Williams, Gordon and Maund, 1973). Before transplant surgeons become too enthusiastic, it is important to examine the necessity for machine preservation by comparison with the simpler methods of storage now available.

Early animal work established that progressive damage occurs when isolated kidneys are kept at body temperature (Murray and Holden, 1954) becoming irreversible after 3 hours' storage (Selkurt, 1945). Cooling was shown to be effective in delaying this damage (Levy, 1959; Semb, Krog and Johansen, 1960; Belzer, Ashby and Dunphy, 1967) probably because it lowers the metabolic requirements of the renal tissue, particularly the cortex (Schirmer, 1964; Fisher, Copeland and Fisher, 1967). Temperatures of 5° to 15°C were optimal: lower or higher temperatures failed to protect and may even facilitate damage (Carrel and Lindberg 1938; Lefebvre and Nizet, 1952; Archibald and Cawley 1956; Bogardus and Schlosser, 1956; Mitchell and Woodruff, 1957; Moyer *et al.*, 1957; Dottori Ekeström and Hansson, 1962). Using temperatures within 5° to 15°C however, storage of up to 12 hours was found to be possible with restoration of function (Murray and Helden, 1954; Schloerb, Waldorf and Welsh, 1957; Steuber *et al.*, 1958; Mouzas, 1967, Collins, Bravo-Shugarman and Terasaki, 1969; Hartley, Collins and Clunie, 1971).

These results with simple surface cooling could be reproduced in human renal allotransplantation (Mowbray *et al.*, 1965; Claes *et al.*, 1971; Hume *et al.*, 1972) provided that the initial warm ischaemic time was less than 1 hour. However, at best, only one-quarter of the kidneys functioned immediately, even though two-thirds did so eventually. Because the diagnosis of early rejection is so much easier and its treatment more effective in functioning grafts (Belzer *et al.*, 1972) attempts have been made to improve these results by flushing the kidneys with cold solutions.

This technique leads to more rapid cooling within the organ (Markland and Parsons, 1963; Birkeland *et al.*, 1959), but the composition of the fluid to be used has been the subject of much trial and debate with variable results both in animal experiments (Table I) and in human allografts (Table II). Various pharmacologic agents have been added to the perfusates, and as a logical extension of this idea pre-treatment of the prospective donor has also been examined. Phenoxybenzamine, chlorpromazine, heparin and methyl prednisolone have all been given to donor animals or patients and the effect on subsequent graft function studied. (Løkkegaard *et al.*, 1971; Pryor, 1972; Bell, Quin and Calman, 1974). Again variable results have been obtained.

Because of these controversial results, both in animal experiments and in clinical transplantation, we have analysed retrospectively results obtained in 200 consecutive cadaver renal allografts. The graft function has been compared with the donor pre-treatment, if any, the type of preservation used for the graft, and the immediate postoperative management of the recipient (Table III).

Table I

Results of Preservation of Dog Kidneys for Variable Periods of Time with Varying Solutions.

Author	Solution	Additives	Range Cold Time (Minutes)	Range Warm Time (Minutes)	Total Number	% Instant Function	% Delayed Function	% Non-function
Dempster *et al.*, 1964	Rheo	Dog plasma papaverine sulphate procaine hydrochloride dipyridamole	360	20	6	100	0	0
	Rheo		360	30	6	100	0	0
Smellie *et al.*, 1970	C4	...	24-30 hours	...	10	40	0	60
Liu *et al.*, 1970	C5	Amino acids and vitamins in 199	48 hours	...	10		80	20
Scott *et al.*, 1970	C4	...	24 hours	15	4	50	0	50
Collste *et al.*, 1970	Extracellular sol	...	24 hours	...	4	0	0	100
	Intracellular sol	...	48 hours	...	13	92	0	8
Frost *et al.*, 1970	C4	...	720	...	4	100	0	0
	C4	...	720	15	5	0	0	100
Sinha *et al.*, 1971	C4	No procaine or heparin	24 hours	23-27	8	50	0	50
	C4	As above—less sodium bicarb.	24 hours	23-27	10	100	0	0
	C4	With procaine and heparin	24 hours	23-27	10	90	0	10
Liu *et al.*, 1971	Hanks 199	Non electrolytes of C5	48 hours	10-15	4	0	0	100
	C5	...	48 hours	10-15	4	100	0	0
	C5	Medium 199	48 hours	10-15	4	60	40	0
Collins *et al.*, 1971 (a)	Perfudex		24 hours	Minimal	4			
	Buffered perfudex	Heparin and procaine	24 hours	Minimal	5	?	?	?
	Plasma	Heparin and procaine	24 hours	Minimal	4			
	C3	Heparin and procaine	24 hours	Minimal	9			
Woods *et al.*, 1971	C4	...	24 hours		6	100		0
	Ringers	...	24 hours		6	33		67
	Plasma——→	Freeze thawed filtered	24 hours		6	67		33
Johnson 1972 (a+b)	C4	...	24 hours	0-3	5	100		0
	C4	...	24 hours	30	8	25		75
	C4	...	24 hours	40	2	0		100
Collins *et al.*, 1973	C3	Various	24 hours	...	59		97	3
Sachs *et al.*, 1973	Two hyperosmolar solutions	...	2-3 days	3-30	18	100		
		...	120-180	3	12	100		
	...							
Quin *et al.*, 1973	Gelin method		360	40	7	14		86
	B.S.S.D.		360	40	6	33		67
	(like perfudex)		360	40	10	30		70

Methods

Donor Pre-treatment

In all cases, 25,000 units of heparin were given immediately before or just after cardiac arrest. In groups 4 and 5 (Table III) phenoxybenzamine 100 mg was given at the time the ventilator was switched off, or immediately after cardiac arrest in those donors not on a ventilator. In the "ventilator switch-off" situation the heart continued to beat for up to 40 minutes in many of these donors, but at no time was the drug administered as much as 2 hours before cardiac arrest as reported by Bell (1974).

In all cases, if cardiac arrest had occurred before the drugs were administered cardiac massage was carried out for 2 to 5 min to ensure that the drugs reached the kidneys.

Treatment of the Kidney

We have divided our kidneys into 5 groups (Table III).

Group 1: The majority of these kidneys were harvested by F. G. E. but a few were taken by M. B. and others received from St Mary's Hospital, Paddington. The kidneys were stored by simple surface cooling. They had heparin pre-treatment but no specific recipient postoperative treatment.

Group 2: These kidneys were received from other centres, using a cold Rheomacrodex flush. The donors had heparin pre-treatment only and all recipients received specific postoperative treatment.

Group 3: These kidneys were received from a variety of centres including our own and were flushed with either Gelin's, Perfudex or Collins' C4 solution. All received heparin pre-treatment. We were able to subdivide this group into Group 3A, in which the recipients did not have any specific treatment and Group 3B where specific recipient treatment was carried out.

Group 4: These kidneys were taken by surgeons associated with the S.E. Renal Units and the majority by one surgeon. All donors were pre-treated with heparin and phenoxybenzamine and all recipients received specific treatment.

Group 5: These kidneys were received after variable times on a Gambro machine either at St Bartholomew's Hospital or King's College Hospital. This is a very mixed group. Some of the donors were pre-treated with heparin and phenoxybenzamine and some of the recipients received phenoxybenzamine and frusemide.

It is important to note that these groups are not directly comparable because the kidneys were harvested by a variety of surgeons in a variety of centres using different surgical techniques. No specific policy was taken as to which group any particular kidney belonged prior to implantation and, indeed, the majority of kidneys in Group 1 were transplanted prior to 1970, whereas those in the rest of the groups were transplanted since that date. Finally, the surgeon responsible for re-implantation of Group 1 kidneys was F. G. E. whereas the majority of the kidneys in the other groups were implanted by M. B. Thus, the kidneys in Group 4 had the most constant treatment. They were harvested and implanted by one surgeon.

Postoperative Specific Recipient Treatment

Circulating volume

When the Transplant Unit was started we were concerned because using simple surface cooling techniques we could not get immediate graft function; whereas at St Mary's Hospital, Paddington, where exactly the same technique was used a proportion functioned immediately (personal communication, Hume, 1969). In an analysis of our combined results it was discovered that, at that time, many of the patients from St Mary's Hospital were on peritoneal dialysis and therefore had relatively higher fluid load and a higher blood urea (*i.e.* a higher plasma osmolarity) than our own patients maintained on haemodialysis. This evaluation suggested that we should try to increase the fluid and osmotic load during the postoperative period. Using a central venous line we

Table II

Results of Preservation of Human Kidneys with Variable Ischaemia Times and Various Flushing Solutions.

Author	Solution	Additives	Minutes: Range: Cold Time	Minutes: Range: Warm Time	Total Number	% Instant Function	% Delayed Function	% Non-function
Brunius *et al.*, 1968	Rheo	...	135-337	16-30	21	86		14
	Rheo	...	135-425	31-45	8	86		14
	Rheo	...	105-295	46-60	9	89		11
Sells *et al.*, 1970	Ringer	Albumin and heparin	83	97	48	73		27
	Rheo	Fructose bicarb.	Mean time 259	Mean time 87	43	67		33
Hartley *et al.*, 1971	C3	...	Mean time 16	Mean time 357	29	83	10	7
Collins *et al.*, 1971	Herman's sol	...	Mean time 121	Mean time 16-17	4	0	0	100
	C3	...	Mean time 343	16-17	14	86	14	0
Collaborative study— Paris 1972	C3	...	Mean time 0-120	0-60	60	55	18	27
	C3	...	120-360	0-60	63	62	6	32
	C3	...	360-540	0-60	39	40	31	29
	C3	...	540-960	0-60	26	44	Not known	
G. Williams *et al.*, 1972	Rheo	Fructose bicarb.	0-600	0-60	26	31	31	38
	Rheo	Fructose bicarb.	0-600	60-100	72	16·5	53	30·5
	Rheo	Fructose bicarb.	0-600	7100	42	2	62	36
Clark *et al.*, 1973	Not Collins	...	0-20 hours	0-30	117	44	31	25
	Not Collins	...	0-20 hours	>30	19	42	26	32
	Collins	...	0-20 hours	0-30	108	63	19	18
	Collins	...	0-20 hours	>30	10	30	30	40
Cullum *et al.*, 1973	Perf and Rheo	...	...	...	82	50	35	15

Table III

Groupings of 200 Cadaver Kidneys in Relation to Donor Pre-Treatment, Preservation Technique, Ischaemia Times and Recipient Postoperative Treatment.

Groups	I	II	III	IIIa	IIIb	IV	V
Donor pre-treatment							
Heparin	+	+	+	+	+	+	+
Phenoxybenzamine	–	–	–	–	–	+	±
Kidney treatment	Surface cooling	Flushed with colloid solution	Flushed with crystalloid solution	as III	as III	Flushed with crystalloid solution	Flushed with crystalloid solution and machine perfusion
Initial warm ischaemia	35	23	27	27	26	25	32
Mean and range (in min)	11-72	10-45	0-145	1-145	0-70	3-55	5-80
Cold ischaemia	154	554	361	427	142	276	827
Mean and range (in min)	19-390	140-401	52-1265	95-1265	52-420	55-732	211-920
Operative time	34	23	25	24	32	25	28
Mean and range (in min)	15-60	15-26	13-45	15-40	15-50	15-50	10-45
Recipient: frusemide and fluid load	–	+	±	+	–	+	±
Number of kidneys	28	14	60	46	14	78	20

maintained their venous pressure at 5-10 cm of water. If the blood urea at the time of operation was less than 100 mg/100 ml then 10 to 20 g of Mannitol was infused after release of the vascular clamps.

Phenoxybenzamine

One of the problems of obtaining a good perfusion of the kidney postoperatively is the cold-induced vascular spasm, especially within the renal cortex. To reduce this 100 mg of phenoxybenzamine was given intravenously as soon as the kidney had been re-vascularised.

Frusemide

Hook *et al.* (1966) and Birtch *et al.* (1967) showed that frusemide could increase the renal cortical blood flow. Cantarovitch *et al.* (1971, 1973), in acute renal failure and Bauditz and Klosterhalfen (1971) and Fernando *et al.* (1973) in renal allotransplantation, have shown that large doses of frusemide could increase the renal blood flow and promote a diuresis. We thus gave frusemide, 500 mg at the time of operation. Subsequent doses of up to 500 mg were given 6 hourly to maintain the urine output at 200 ml per hour. If, after 24 hours, there was minimal output then the frusemide "drive" was removed. In some patients after the initial dose there was a massive diuresis. This was controlled by transfusing with colloidal fluid (usually blood) with added sodium and potassium to maintain the electrolyte balance. If only crystalloid solutions were used the urine output would continue to increase and one was continually "chasing" the urine output. More recently this regime has been modified so that the frusemide is given by continuous infusions starting at 2 mg per minute.

Dialysis

If, after 24 hours, there had been no adequate urine output the maintenance of the venous pressure was removed and the frusemide drive stopped. The patient was then dialysed as necessary,

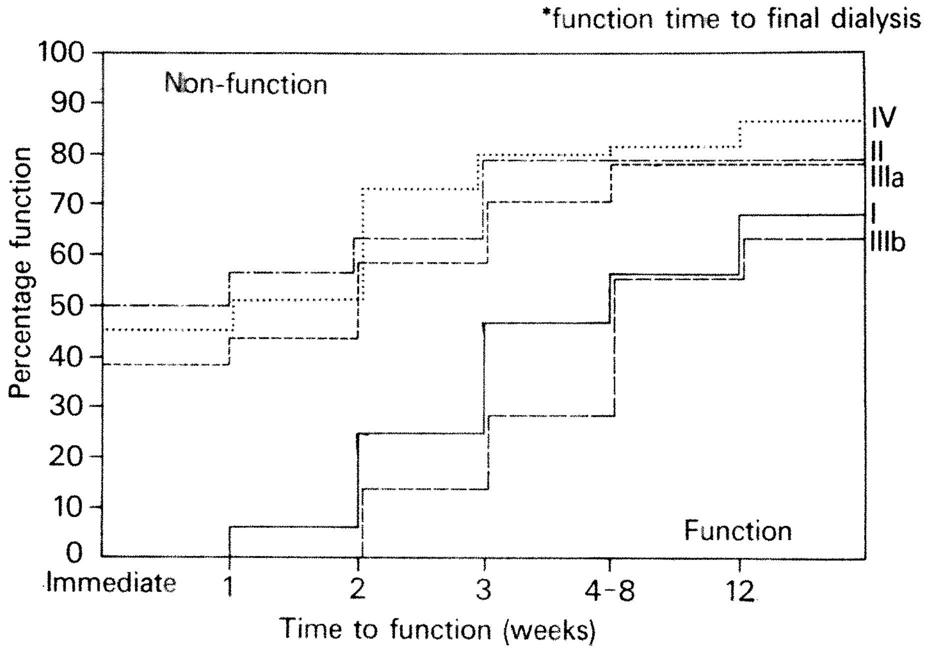

Fig. 1. Representation of Table 4. Time to function* in cadaver kidneys using different preservation and patient management.

usually 8 hours 3 times a week on a Travenol R.S.P. with a CF 100 coil, until adequate renal function was obtained.

Results

Table III shows the ischaemia times of 200 consecutive cadaver kidneys. Table IV analyses their percentage function, represented diagrammatically in Figure 1. It should be noted that throughout time "to function" was taken as the day of last dialysis. In the majority of cases this meant that the blood urea and serum creatinine rose for a further 1 to 2 days and then began to fall.

There is little difference in the 5 groups between the initial warm times and the operative time, but the cold times in Groups 2 and 3 are slightly longer than in Groups 1 and 4 because these kidneys had to travel from other centres, but statistically only Group 2 gave significantly longer cold times. Group 5 kidneys have much longer cold times because of the time on the preservation machine and these are not included in the statistical analysis.

There is no difference between the eventual function rate in all groups except the perfused kidneys. There is, however, a significant difference ($P<0{\cdot}02$) in the percentage showing primary non-function in Group 4. This is defined as those kidneys which never achieved adequate function due either to technical reasons or early rejection.

There is also a significant difference in Groups 2, 3A and 4 compared with Groups 1 and 3B in the immediate function rate ($P<0{\cdot}001$). In Group 3, *i.e.* those kidneys where the donor received heparin and the kidneys were flushed with a crystalloid solution, recipients who received a fluid load and frusemide drive had 39% immediate function rate, whereas none of those (albeit a smaller group) in whom there was no similar recipient treatment functioned immediately. If a kidney fails to function immediately there is no statistical difference in Groups 1 to 4 in the time at which the kidneys start to function.

Table IV

Percentage Immediate, Delayed and Non-function in each of the Groups and the Time for those with Delayed Function to work.

	Percentage						
	I	II	III	IIIa	IIIb	IV	V
Function	68	78·5	75	78·5	64·5	86	40
Failed	32	21·5	25	21·5	35·5	14	60
Immediate	0	50	30	39	0	45·5	20
1 week	7	7	3·5	4·5	0	4	0
2 weeks	18	7	15	15	14·5	22	10
3 weeks	21·5	14·5	13	13·5	14·5	5	10
4-8 weeks	10·5	0	5	6·5	28·5	2·5	0
– 12 weeks	11	0	8·5	0	7	5	0
Total number of kidneys	28	14	60	46	14	78	20

Table V

Warm Ischaemia Times in Relation to the Groupings.

	Percentage						
	I	II	III	IIIa	IIIb	IV	V
Warm time 0-30 min	50	85·5	75	74	78·5	81	65
Immediate function	...	50	23	32	...	38·5	10
Warm time 30-60 min	46·5	14·5	18·5	19·5	21·5	19	25
Immediate function	...	...	3·5	4·5	...	9	10
Warm time 60-90 min	3·5	...	6·5	6·5	...	...	10
Immediate function	...	...	1·5	2·5	...	...	
Total number of kidneys	28	14	60	46	14	78	20

Table V relates the warm time to the time of immediate function and shows that there is no statistical difference in any of the groups, excluding Group 5, provided the warm time is less than 60 min. No analysis was made of those kidneys with 60 to 90 min because there were too few to include.

In this series the results with the machine-preserved kidneys, Group 5, are extremely poor. It should be pointed out, however, that many of these kidneys were from a machine which had been inadequately assessed and the actual technique of perfusing inadequately understood. These results emphasise the point that machine preservation is not as easy as it seems or the manufacturing firms make out.

Discussion

From these results it appears that in human allografted kidneys donor pre-treatment is important (Lotke and Schwartz, 1970; Pinkerton *et al.*, 1972; Miller and Alexander, 1973; Miller *et al.*, 1974). Bell *et al.* (1974) have investigated a number of drugs which can be used at various times prior to donor cardiac arrest; and although there is considerable discussion about the ethics of this practice we think that our results justify the use of phenoxybenzamine and heparin. In the future we feel that phenoxybenzamine should be given earlier and combined with methyl prednisolone 0·5—1 gr before cardiac arrest. The argument, that switching off the ventilator is in fact "a trial off the ventilator" and the patient may recover, therefore drugs should not be given, is contradicted by the fact that already the majority of surgeons give heparin at the time of ventilatory arrest. Since many of these patients have had head injuries or cerebro-vascular accidents, it would, on this argument, be unjustified to give the heparin. Once a potential donor has been carefully assessed as being cerebrally dead and permission has been granted for the removal of the kidneys, it seems proper to make sure that the kidneys are in the best state for transplantation, for the sake of the well-being of the potential recipients.

From our figures, it looks as though there is little difference between a crystalloid and a colloid solution flush. It may be that we have in our series the partial benefits of each solution and the Sachs, Petritsch and Kaufman (1973) solution would combine these. Unfortunately, there are problems with the solubility of magnesium in the Sachs solution, but recent evidence from Sachs (Sachs, Petritsch and Kaufman, 1974), Whittembury, Gonzalez and Acquatella (1973) and Calne *et al.* (1974) suggests that the magnesium sulphate and magnesium chloride could be omitted.

There has been some criticism of the fluid load/frusemide drive technique in recipients. Moorhead (personal communication, 1973) using a modification of this technique, obtained enormous urine outputs and considerable difficulty in controlling the recipient's electrolyte balance. It must be stressed that this will occur if crystalloid solutions alone are used to maintain the fluid balance. The dose of frusemide must be regulated to keep the output at approximately 200 ml per hour. This is an arbitrary figure, but in patients in whom this level of output was not maintained we found that after 24 to 48 hours the urine output would gradually fall off and the patient would need dialysis for a further 10 to 14 days. Blood is by far the best solution, alternating with saline to maintain the vascular volume. This will act to maintain the osmolarity of the vascular and interstitial fluids without acting as a diuretic. It will encourage a good renal blood flow and help to counteract the tendency of the plasma potassium to fall. Whole blood should be used, not washed cells since the patient needs volume as well as haemoglobin. At present, there is no evidence that whole blood in this situation causes sensitisation of the patient. Indeed, there is evidence to the contrary in that white cells given at this stage or immediately prior to transplantation may inhibit the rejection of the graft (Calne *et al.*, 1966, 1970; Linn, 1966; Wilson *et al.*, 1969).

Finally, we come to the problem of the machine-perfused kidneys. In our series the results of the machine-preserved kidneys (Group 5) are poor. Each individual machine, before use in the human situation, should be assessed with animal kidneys to establish the exact technique. It is significant that Stephenson *et al.* (1973) were unable to reproduce the results of Claes *et al.* (1972, 1973) using identical Gambro machines, nor could Williams *et al.* (1972, 1973) reproduce the results of Belzer (1972) using a Belzer machine.

It should be emphasised that from the results in Groups 2, 3, and 4 kidneys can be stored up to 12 hours using a colloid or crystalloid flush with 75·8% to 86% function rate and a 45 to 50·05% immediate function rate. It still leaves a 14% to 21·5% primary failure rate. This, together with the increased need for cadaver kidneys and thus the necessity of attempting to use kidneys from donors in whom the renal function, immediately prior to death, is inadequate results in a need for some "*in vitro*" assessment of renal viability. Longer terms of preservation are also needed for more esoteric tissue-matching techniques (*e.g.* mixed lymphocyte culture), to enable kidneys to be transported over greater distances around Europe, to allow the kidneys to be transplanted on routine operating lists and to enable, if necessary, the recipient's clinical condition to be improved for the operation. Further, machine preservation would also allow the kidney to be perfused with a variety of agents with the object of increasing the chances of immediate function and reducing the incidence of early rejection.

It is therefore necessary that research into machines which can safely preserve kidneys for long periods of time, to enable viability to be evaluated and to ensure immediate function of the kidney, should continue. Machine preservation of kidneys will be the future method but at the moment simple intra-arterial flushing seems to be best for short-term preservation.

Summary

200 consecutive human cadaver kidneys were preserved using 6 different techniques.

Some attempt was made in the clinical situation to assess donor pre-treatment and postoperative specific recipient treatment to encourage immediate renal function.

Provided the warm time was less than 60 min and the cold time less than 12 hours, intra-arterial flushing with a crystalloid or colloid solution combined with pre-treatment of the donor and postoperative fluid load/frusemide drive to the recipient gave the best results.

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Short Case Report

Solitary Crossed Renal Ectopia

Solitary crossed renal ectopia is a very rare anomaly. So far only 16 patients have been reported in the world literature (Norman *et al.* 1973). A patient with this anomaly is reported.

Case Report

A young patient was admitted in C.M.H., Rawalpindi, with dull and localised pain right lumbar region, which did not radiate to any other area. Plain X-ray abdomen showed two radiopaque stones in right renal area and fused lumbar hemivertebrae (Fig. 1). Intravenous pyelography showed a hydronephrotic right kidney with renal calculi.

On cystoscopic examination the ureteric opening on the right side was absent. Left ureteric opening was normal. A ureteric catheter was passed and ascending pyelography was done which showed solitary crossed renal ectopia (Fig. 2).

Comment

This case is interesting in that renal calculi were associated with this very rare type of congenital anomaly. Crossed ectopic kidney receives its blood supply from the lower aorta or iliac vessels. The case reported by Norman *et al.* (1973) received its vascular supply from the aorta at an unusually high level. However our case was not investigated by arteriography.

I owe my thanks to Major General M. S. Hassan, Consultant Surgeon, Armed Forces, and Colonel Mahmud-ul-Hassan for helping me in preparing this paper and allowing me to publish it. My thanks are due to Lieutenant-Colonel M. Saeed Malik for carrying out the radiological investigations of this case.

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Reference

NORMAN, W. J. and ADAM, M. (1973). Solitary crossed renal ectopia. *British Journal of Urology*, **45**, 480-481.

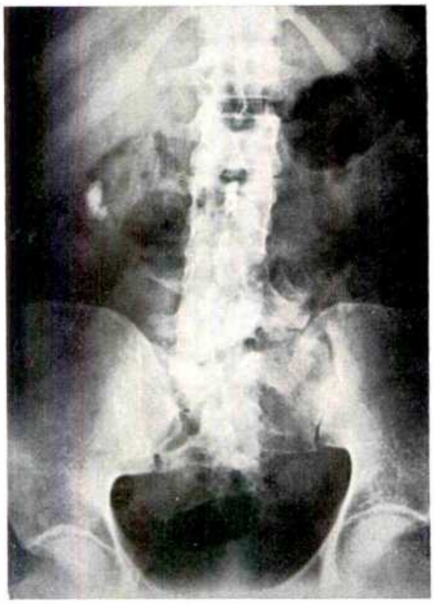

Fig. 1.

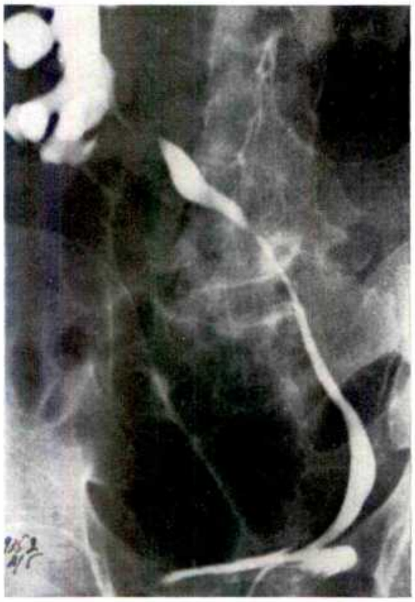

Fig. 2.

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Urinary Tract Infection and Wound Infection in Kidney Transplant Patients

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In human renal transplantation, the most frequent complication next to rejection of the transplant is infection of the urinary tract and wound infection. Several reports indicate that 60% to 90% of kidney transplant patients develop urinary tract infection within the first 3 to 6 months (Kelly *et al.*, 1967; Prout *et al.*, 1967; Leigh, 1969; Bennett *et al.*, 1970; Sussman and Russell, 1972).

The aim of the present study was a retrospective evaluation of the frequencies of urinary tract infection and wound infection in a Scandinavian transplantation centre, where the transplants were almost exclusively cadaver kidneys from donors who underwent nephrectomy after cessation of heart action. Furthermore, it was found of value to examine in particular the relationship between infections and indwelling catheters and drains.

Material and Methods

The report comprises all patients who underwent transplantation in the period from August 1970 to May 1973 and covers the first 3 months after the transplantation. The occurrence of urinary tract infection 6 months after operation was also evaluated.

The investigation comprises 53 transplantations in 51 patients, 24 women and 27 men. 12 of the patients had chronic pyelonephritis, 19 had chronic glomerulonephritis, and the remainder had either cystic kidney, nephrosclerosis or some more common disease.

Only a few of the recipients had undergone nephrectomy and only 1 patient received the kidney transplant from a living donor.

Technique of Catheterisation and Drainage

Immediately before the operation, a urethral catheter was introduced under sterile drapes. The external genitals were washed with chlorhexidine 0·02% and the urethra was disinfected with chlorhexidine gel 0·1%. The bladder was emptied and the urine examined bacteriologically, and the bladder then rinsed with chlorhexidine 0·02%. The catheter was connected to a sterile closed container. During the operation, a catheter was inserted in the ureter of the transplanted kidney and connected to a sterile closed urimeter via the bladder and abdominal wall. The operation wound was drained by 2 suction drains placed at the vascular anastomoses and at the bladder ureter anastomosis, respectively. The ureteric catheter was removed if non-functioning, or around the 8th day, and the urethral catheter was usually removed on the 8th to 10th day. The suction drainage was terminated when the secretion ceased.

Immunosuppressive Treatment

The immunosuppressive therapy was started immediately before the operation, with azathioprine (Imuran ®) 300 mg. During the operation, methylprednisolone was given (Solumedrol ®), 1 g i.v. Azathioprine, 100 to 150 mg, was administered orally daily from the 1st postoperative day, and in addition prednisone 200 mg daily from the 3rd postoperative day, tapered off to 20 mg by the 90th postoperative day.

Bacteriological Investigation

During the period of catheterisation, cultures were made daily. After the removal of the catheter, cultures were made twice a week from the mid-stream urine or on each occasion of outpatient control. The urine was cooled to

Table I

Number of Days following Transplantation before Development of Urinary Tract Infection

Days	Female	Male	Total	Total in per cent
0–3	9	3	12	25
4–14	13	10	23	50
15–33	2	7	9	20
34–90	0	2	2	5

4°C immediately after collecting and dispatched to the laboratory. Here the samples were cultured quantitatively using calibrated loops (Vejlsgaard, 1973). Urinary tract infection is defined as the occurrence of 100,000 bacterial colonies per ml urine. After removing the drain, the tip of the drain was sent for bacteriological investigation. Cultures were made from the wound on clinical signs of infection and likewise from abscesses. Culture was by conventional bacteriological technique.

Results

Urinary Tract Infection

6 patients had bacteriuria prior to the transplantation. Postoperatively, 5 of these patients produced urine and developed bacteriuria immediately.

Of the 47 patients who produced urine after the operation, 46 developed bacteriuria within the observation period.

Urinary tract infection developed at an early stage after the transplantation, thus 25% developed infection within the first 3 postoperative days. During this early period there was a considerable preponderance of women. Later there was a preponderance of men as shown in Table I.

Relationship Between Urinary Tract Infection and Catheterisation

On the occasion of the first urinary tract infection, 20 out of 25 patients had an infected ureteric catheter, and all had infected urethral catheters. 10 patients had only a urethral catheter on first infection and 11 did not have catheters at the time of infection.

Table II shows the bacterial species in the individual patients on the occasions of the first 4 urinary tract infections. *E. coli* and *Streptococcus faecalis* were the bacteria which occurred most frequently in the urine, both on first infection and on recurrent infection.

6 months after the transplantation, there were 27 functioning kidneys. Bacteriuria was present in 9 cases, and 17 cases were under treatment for urinary tract infections. At this stage the catheters had been removed in all cases.

Treatment

38 patients received treatment on the basis of sensitivity determinations, and 28 developed sterile urine following the first treatment. Of the 8 who were not treated, 2 developed sterile urine after removal of the catheter and 4 after removal of the transplant. 2 patients developed sterile urine spontaneously.

Wound and Drain Infection

Only 9 of the 53 transplantations did not develop infection of the drain or wound. The drain was infected in 36 patients. Wound infection was demonstrated in 18 patients and abscess formation in addition in 9 of these.

Table III shows the bacterial species in the various infections. *Staph. aureus* was a frequent cause of the wound and abscess infections, and in one-third these developed without any infection being found in the drain tips. About half of the wound and abscess infections with *E. Coli* likewise developed without any preceding infection of the drain tip.

7 drain tips were infected with *Staph. albus* alone, and none of these patients subsequently showed wound infection of abscesses. In contrast to this, 15 cases of wound infection developed in 19 patients in whom the drain tips had been infected with other bacteria than *Staph. albus*.

In 9 patients, the same species of bacteria was found in the urinary tract infection, in the drain infection, and in the wound or abscess infection.

Only 1 patient in the present material developed bacteriaemia from a recurrence of a gastrocolic fistula from a previous splenectomy.

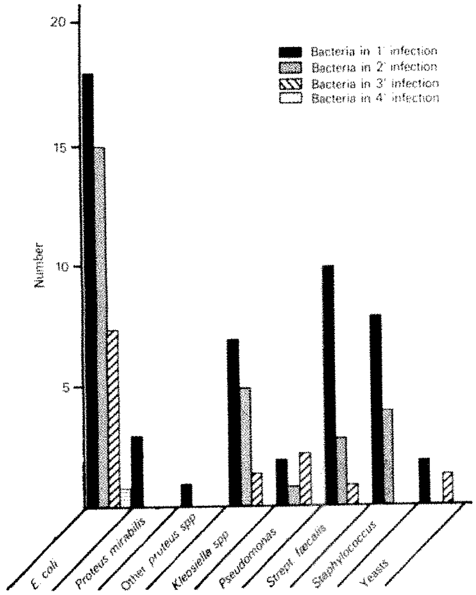

Fig. 1. Bacteria in the first 4 urinary tract infections after transplantation.

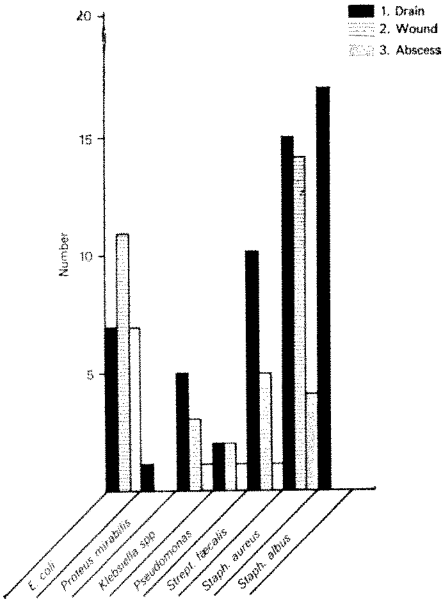

Fig. 2. Bacteria in wound infections.

Discussion

Bacteriuria occurs with 70% to 90% incidence among patients who have received cadaver kidneys (Kelly *et al.*, 1967; Prout *et al.*, 1967; Leigh, 1969; Bennett *et al.*, 1970; Sussman and Russell, 1972). When the kidney was removed with the heart still beating, the rate of infection found was not definitely lower (65% to 74%) (Kelly *et al.*, 1967; Prout *et al.*, 1967; Bennett *et al.*, 1970). The infection could conceivably be transmitted with the cadaver kidney, but Sussman and Russell (1972) found no transmission in 7 cases where significant bacteriuria was present in the donor. Martin (1969), however, reports a case of infection with Klebsiella following transplantation of a kidney from a donor who had died from Klebsiella meningitis. Leigh (1969) and Martin (1969) report that the underlying disease in the recipient also has significance for the infection, as patients with chronic pyelonephritis develop bacteriuria more frequently than patients with chronic glomerulonephritis. We could not demonstrate this difference, but of the 6 patients in the present material who had infection prior to the transplantation, 5 who produced urine postoperatively developed bacteriuria immediately, with the same bacterial species. However, the postoperative infections were no more severe than in those patients with a primarily sterile urinary tract.

In the majority of series it has been shown that the infection takes place via the urinary catheter (Kass and Schneidermann, 1957; Brehmer and Madsen, 1972). Following a single catheterisation, the risk of infection is 2% to 4% (Kass, 1957) but with catheter drainage of 2 to 3 days duration, a frequency of infection has been found of 52% to 88% (Paterson, Barr and MacDonald, 1960; McFayden and Simmons, 1968). By employing a careful aseptic technique of catheterisation, disinfection of the urethra with chlorhexidine gel and periodic flushing of the bladder with chlorhexidine, as well as use of closed drainage, it is possible to reduce the frequency of infection to one third (Gillespie *et al.*, 1962; Clark and Crossley, 1973; Gillespie *et al.*, 1967).

Just as in the present investigation, Leigh (1969) found that there was a considerable preponderance of women in the group with early infections, and that 65% of the bacteria isolated were originating from faeces. Both these observations might suggest that the infection ascends along the urinary tract, via the catheter.

Sussman and Russell (1972) demonstrated that 34% of those patients who had bacteriuria developed sterile urine within the first 24 hours after the removal of the urethral catheter. Similar conditions could not be demonstrated with certainty in the present material.

Even though infections of the urinary tract are a frequent complication among patients who have received transplants, the incidence is nevertheless of the same order of magnitude as in other series of patients who have received treatment involving catheterisation over long periods, and who were not under immunosuppressive treatment. But of those patients who had a functioning transplant 6 months after the transplantation, 66% were under antibiotic therapy and half of these had an active urinary tract infection, This may be due to the immunosuppressive treatment. The significance of these late infections for the prognosis is unknown.

In some series septicaemia has been a serious and frequent complication. In a report of Kelly *et al.* (1967), 23 out of 57 patients who had received a transplant died from septicaemia. In contrast to this, only 1 case was found in the present material, in a patient with recurrent gastrocolic fistula which had developed previously following splenectomy.

The incidence of wound infection varies considerably. Sussman and Russell (1972) found wound infection in 9%, Bell *et al.* (1972) in 15%, Kelly *et al.* (1967) in 32% and the present authors in 33%. Wound drainage, like bladder drainage, has varied in duration, from 48 hours (Bell *et al.*, 1972) up to 8 to 10 days in the present material. The number of wound infections in the present material is high, and is probably due to the prolonged drainage.

The present material includes 9 cases with the same bacterial species in the urine, drain, wound or abscess. It cannot be determined with certainty, however, whether the infection spreads along the urinary tract and transplant or whether it spreads via the wound surface or drain.

Wound infection developed in 15 out of 19 cases of drain tip infections with other bacteria than *Staph. albus*. The necessity of instituting treatment should therefore be considered immediately the drain tip gives a positive culture, and in particular it is necessary to determine whether a deep infection and abscess is in process of developing.

Conclusion

Of the 53 persons who in the present study received kidney transplants only 1 avoided urinary tract infection postoperatively. All the infections except 6 probably arose via indwelling catheters in the bladder and ureter. Moreover a high frequency of reinfections took place but without serious complications. The current use of cadaver kidneys did not imply a higher frequency of urinary tract infections compared to previous results of transplantation with kidneys from living donors. The wound drainage employed was also accompanied by a high frequency of wound infections and abscess formation. If possible wound drainage should be avoided or should be of very short duration, as the infections seems to take place via the drains.

Summary

The frequency of urinary tract and wound infections was studied in 53 patients most of whom had received kidneys from donors without heart action.

Urinary infection was demonstrated soon after the transplantation in 46 out of 47 with functioning kidneys. Recurrent infections took place during the first 3 months and still half of the patients were infected or under treatment 6 months after the operation. The urinary infection seems mainly to arise via indwelling catheters.

Wound infections were demonstrated in 18 out of the 53 patients and in addition abscess formation took place in 9 of these. In the majority of the infected wounds previous infected drains were demonstrated. In all, 36 of the patients had infected drains, the use of which therefore is to be avoided.

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Short Case Report

Primary Amyloidosis of the Ureter: Case Report

Primary amyloidosis is rare in the urinary tract, usually involving the bladder. 9 previous cases of solitary ureteral involvement have been reported (Johnson and Ankenman, 1964; Magri and Atkinson, 1970; Takaka *et al.*, 1971).

Mrs V. A., a 65-year-old woman, noted haematuria 3 months prior to consultation, in December 1972. Past health, physical examination, urinalysis and urine cultures were negative.

IV urograms showed narrowing of the lower left ureter and hydronephrosis. Cystoscopy was negative. Retrograde pyelograms (Fig. 1) confirmed the narrowing of the ureter. Chest X-ray and urine cultures for tubercle bacilli were negative.

Haematuria recurred and nephro-ureterectomy was performed in October 1973 with the presumptive diagnosis of ureteral tumour.

Examination of the specimen showed a granular haemorrhagic lesion of the lower third of ureter 6 cm in length with ulceration. Microscopy with Congo-Red stain (Fig. 2) showed replacement of muscle by amorphous eosinophilic material with a chronic inflammatory reaction and multinucleated giant cells. Blood vessels and adjacent fat were involved.

Postoperatively, systemic Congo-Red tests and bone marrow aspirate were negative for amyloid.

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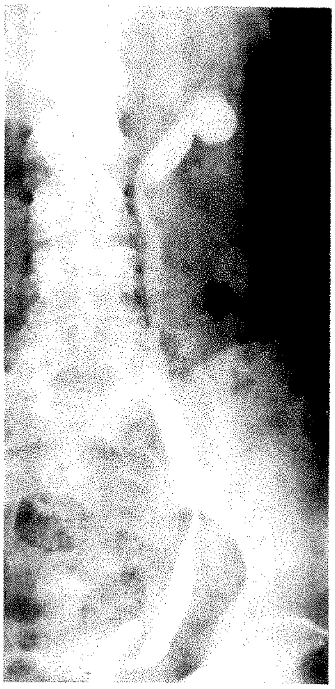

Fig. 1

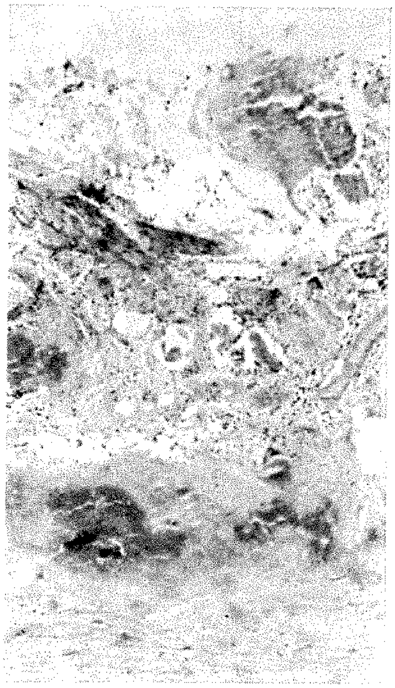

Fig. 2. Microscopic section through involved ureter showing amyloid deposits.

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Trans-uretero-ureterostomy: British Experience*

IRVINE B. SMITH and JOE C. SMITH
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Trans-uretero-ureterostomy is a clumsy name for a simple operation joining one ureter into the other. Although Boari's experiments with this procedure failed (Casati and Boari, 1894), Monari (1896) succeeded soon afterwards using side-to-side anastomoses. The first such operation on man came 40 years later (Higgins, 1934) but was a brilliant success, producing a normal IVP after another 33 years (Madden, Tan and McCann 1967). Since 1953 Hodges and his colleagues in Oregon have published details of 76 personal operations and now consider that the procedure is wrongly neglected (Anderson *et al.*, 1959; Udall *et al.*, 1973). However, British surgeons still remain wary of interfering with a healthy ureter and kidney on the opposite side. In 1947 Slutsky first reported the successful drainage of a solitary kidney deprived of its own ureter by using the spare ureter on the opposite side.

The present paper has 3 aims: to assess the collective experience of British and Irish surgeons; to test a preliminary British claim that the operation is safe and sound and could be used more frequently (Smith, 1969); and to search for any evidence of damage to the opposite (receiving) ureter and kidney.

Experience of British Surgeons. 158 replies were received from 300 questionnaires sent to members and associates of the British Association of Urological Surgeons (Table I). Altogether, 45 surgeons had done 141 trans-uretero-ureterostomies. Only 2 surgeons said they would never perform this operation, although 4 others had reservations, considering it potentially dangerous for the intact ureter and kidney. The 107 other surgeons who had not actually done this operation were nevertheless prepared to do so under certain conditions.

Table I

158 Replies to 300 Questionnaires sent to Members and Associates of the British Association of Urological Surgeons in 1973

29	surgeons had done Y-anastomoses above a diversion operation
25	had done simple Y-anastomoses
5	had drained a solitary kidney via the opposite ureter
113	had not done a trans-uretero-ureterostomy
2	never would
4	were very doubtful if they ever would

Reasons for not Operating. Of 113 surgeons who had avoided this operation, 66 offered 89 reasons for doing so (Table II). The majority preferred their familiarity with some other method, especially the Boari flap or psoas hitch; many had never been presented with a suitable indication; and others were put off by fear of damaging the intact kidney or ureter on the opposite side. The remaining 47 surgeons did not specify their reasons.

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*Paper read to the British Association of Urological Surgeons in Birmingham, October 1973.

Table II

89 Reasons for avoiding Trans-uretero-ureterostomy given by 66 Surgeons

Operation never indicated		29
Preference for other operation		
Boari flap	14	
Ileal ureter	8	
Psoas hitch	7	
Nephrectomy	5	
Rejoining the ureter	3	
Ligation of ureter	1	
	—	38
Fear of damaging the other kidney		19
Too complicated		2
Fear of stricture		1
		—
		89

Table III

The Indications for 56 Simple Trans-uretero-ureterostomies

Deliberate excision with a carcinoma		
Bowel	12	
Ureter	6	
Bladder	2	
Gynaecological	2	
	—	22
Accidental injury		16
Stricture		10
Irradiation		3
Failed reimplantation		3
Bilateral neurogenic hydroureter		1
Not stated		1
		—
		56

Operations Performed. The indications for and the results of altogether 141 operations have been analysed—114 from questionnaire replies and 27 performed by the 2 authors. These operations have been categorised as follows:

(1) 75 Y-anastomoses performed by 29 surgeons as part of a urinary diversion. This procedure is widely accepted and will not be considered further in this paper.

(2) 56 Y-anastomoses performed by 25 surgeons for obstruction or injury of a ureter above a normal bladder.

(3) 10 cross-over anastomoses performed by 5 surgeons enabling a solitary kidney to drain via the opposite ureter.

56 Simple Y-anastomoses

Indications. This operation is not needed often but in certain conditions is extremely helpful. Its most frequent use has been after a planned excision of some lower ureter while removing carcinoma, usually of bowel, but occasionally of ureter or other pelvic organs (Table III). However, accidental injury also accounted for many Y-anastomoses. Unfortunately these injuries were often referred to a urologist after some delay, thus necessitating a late secondary operation. The operation was also used for several ureteric strictures which were usually due to stone, though one or two were "idiopathic". Ureters damaged by irradiation, failed reimplantations and also bilateral injuries have been treated satisfactorily by trans-uretero-ureterostomy. Vesico-ureteric reflux was not the indication for any of these 56 operations, although Higgins and others have treated reflux successfully in this way.

Contra-indications. Preference should always be given to direct reimplantation into the bladder whenever this is possible. Any disease which might involve both kidneys or ureters should contra-indicate trans-uretero-ureterostomy; obvious examples being tuberculosis, recurrent stone formation or papillomatosis. With this operation, chronic pyelonephritis on one side could possibly endanger the other kidney, but experience has shown that recent acute infections have cleared up quickly with the better drainage established by trans-uretero-ureterostomy. Its use for retroperitoneal fibrosis would be unwise. A baggy, atonic, chronic hydro-ureter should not be drained in this way, but a recently dilated ureter will usually recover well. A patient with one ureter obstructed by inoperable carcinoma in the pelvis has nothing to gain from this operation. Many surgeons

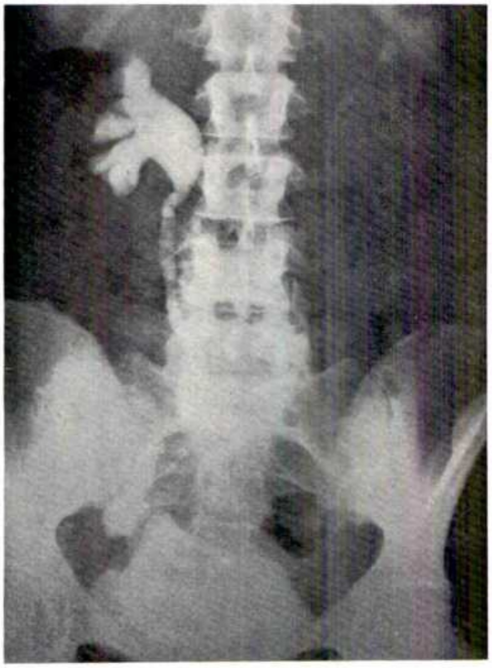

Fig. 1. Case 1. Preoperative IVP, 1 hour after injection.

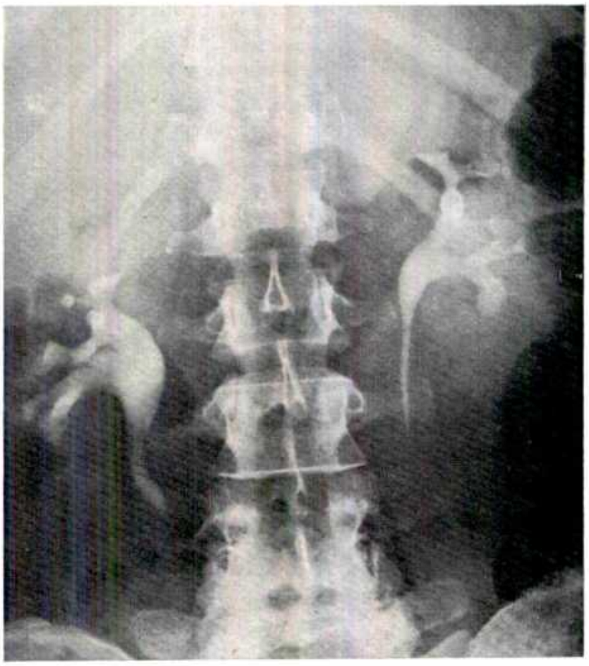

Fig. 2. Case 1. IVP 3 years after operation and 25 mins after injection.

will undoubtedly prefer their personal expertise with a psoas hitch or a Boari flap but we feel that a trans-uretero-ureterostomy is much easier.

Technique. The technique has been described elsewhere (Anderson *et al.*, 1959; Smith, 1969; Udall *et al.*, 1973). The choice of splints or not is largely personal, but good external drainage from around the anastomosis is essential (we have found vacuum drainage reliable), and the bladder should also be drained with a catheter for a week to prevent any back pressure on the anastomosis.

It is important to emphasise that trans-uretero-ureterostomy is technically simple and can be performed easily by any surgeon capable of reimplanting a ureter into the bladder.

Results. The authors' satisfaction with the results of their own 16 Y-anastomoses has been supported fully by the 23 surgeons who did the 40 other operations.

Clinical results were especially good in those patients who had been referred with a distressing or dangerous ureteric fistula after surgery: their cure was quick, simple, effective and usually free from any complication.

Illustrative History. A 40-year-old patient developed a right uretero-vaginal fistula after a total hysterectomy and left salpingo-oophorectomy made very difficult by 2 previous attacks of pelvic peritonitis. After 4 weeks of conservative management she was depressed, anxious and ill. There was a tender mass on the right side of the pelvis and the IVP (Fig. 1) showed dilatation of the right kidney and ureter. Her urine was infected with *B. Proteus.*

At operation the right ureter was easily divided above the pelvic mass, its end spatulated and implanted into the left ureter at the level of L5. A pelvic collection of infected urine was drained. After operation her urinary infection cleared quickly and the fistula dried immediately. Convalescence was uncomplicated although she took some time to recover energy and morale. IVPs taken at 4, 12 and 38 months showed that her right kidney and ureter recovered quickly and almost to normal and that her left kidney and ureter remained quite sound (Fig 2).

Furthermore, and with few exceptions, those patients who underwent planned resection of a ureter also remained quite free from urinary complication after trans-uretero-ureterostomy.

Radiological assessment is based on the postoperative IVPs of 41 patients, 15 of whom had been treated by the authors. In 34 of these patients, the kidney above the resected ureter looked normal and in many cases the radiologist could not identify which ureter had been transplanted. 3 hydronephroses showed marked improvement but not to normal. 3 chronic hydro-ureters treated by this method did not improve. In no single IVP was there any evidence that the opposite kidney had suffered in any way as a result of the anastomosis, apart from the early, mild and temporary dilatation previously noted (Smith, 1969).

Complications. Most surgeons have been impressed by the absence of complications. Urinary leakage has been infrequent and brief except where distal obstruction was present. 4 failures had valid reasons: 1 anastomosis failed to heal because only 7 cm of ureter were available on each side above sarcomatous obstruction complicating polyposis coli and panproctocolectomy (Gardner's Syndrome); 1 anastomosis failed to heal because of a wrong technique employing an approach through the loin instead of across the abdomen; 1 patient with uraemia from advanced uterine carcinoma blocked her anastomosis with blood clot and was allowed to die; and 1 anastomosis done for bilateral congenital hydro-ureters needed subsequent diversion because of atony, stasis and infection. 2 patients died from other causes soon after operation: an 83-year-old woman from bronchopneumonia and a 71-year-old man from coronary thrombosis.

The Advantages of Y-anastomosis. (1) The procedure is very simple. (2) When performed after injury to the ureter, the new operative field is well away from infected or irradiated tissues and the original operation. (3) For the latter reason timing of the second operation is not critical. (4) The kidney above the injured ureter is reliably preserved. (5) The opposite kidney is not damaged. (6) The urothelial lining remains intact throughout. (7) Vesico-ureteric reflux is not a problem. (8) Litigation (which has followed nephrectomy for injury to the ureter, Medical Defence Union, 1973) may well be avoided.

10. Solitary-Kidney Cross-over Anastomosis

This operation proved even more useful than the simple Y-anastomosis and should be considered whenever

(*a*) the ureter below a solitary kidney is severely damaged or has to be excised, and
(*b*) it is found that the opposite ureter is still intact.

Illustrative History. A man of 71 had lost his left kidney from trauma as a child and later worked for 40 years in a tyre factory. Eventually he presented with haematuria from a carcinoma at the lower end of his right ureter. A left ureterogram showed that this ureter was thin but still intact and active after 64 year's isolation. The lower half of his right ureter was excised and its upper half was joined end-to-end to his dormant left ureter as a trans-uretero-ureterostomy. Unfortunately he needed an emergency nephrostomy because of temporary blockage of the splint. Then he had a cardiac arrest. In spite of these complications he recovered well and 1 year later there was no evidence of recurrence, and there was good drainage through a ureter which had never been exposed to industrial carcinogens.

The other 9 patients in this group had similar results from their anastomoses, although experience now suggests that it would be wise routinely to include a temporary T-tube ureterostomy or nephrostomy. However, a number of these patients have already died from recurrent carcinoma. We therefore suggest:

(1) During any nephrectomy *keep all healthy ureter* unless contra-indicated; (2) When faced with the problem of draining a solitary kidney *always look for the opposite spare ureter.*

Summary

158 replies to a questionnaire suggest that many British surgeons remain wary of using trans-uretero-ureterostomy, fearing to risk the opposite ureter and kidney or preferring to use a Boari flap or other operation.

141 (27 personal and 114 reported) cases are surveyed.

56 simple Y-anastomoses performed by 27 surgeons gave very good results, with only 4 exceptions due to wrong indications or techniques. Complications were rare. No damage to any opposite ureter or kidney by the procedure was reported.

10 operations enabling a solitary kidney to drain via the opposite spare ureter were all successful. We recommend that during nephrectomy any spare healthy ureter should be preserved so that, if necessary, it can be used to drain the opposite kidney.

We would like to thank all those surgeons who answered our questionnaire with clinical details and helpful observations.

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Short Case Report

Reversible Lymphomatous Non-obstructive Uropathy

A 47-year-old man received radiotherapy in 1957 for histologically proven reticulum cell sarcoma involving inguinopelvic nodes and again in 1958 for enlarged right cervical nodes. Further manifestation did not occur until April 1970, when he developed renal failure. Serum urea 282 mg/100 ml, creatinine 8 mg/100 ml.

Cystoscopy and retrograde pyelography revealed no ureteric obstruction. The kidneys were enlarged, and the calyces attenuated. It was concluded that the patient had a non-obstructive uropathy caused by renal involvement with reticulum cell sarcoma.

Treatment was with cyclophosphamide (Fig.), causing a fall in the blood nitrogen levels, after a transient rise indicating tumour lysis. Palpable cervical and axillary nodes and slight hepatomegaly regressed. Since this episode the patient continues in remission, on a small maintenance dose of cyclophosphamide, being last seen in March 1975.

Comment

Although renal involvement in the lymphomas is common, uraemia is usually caused by bilateral ureteric obstruction and is due to renal parenchymal involvement alone. Lizzi *et al.* (1971) quoted 16 such cases from other articles and reported 1 case. Survival time was extremely short in all cases. In the case reported here, remission continues at almost 5 years, following simple continuous drug therapy. This response is better than any reported elsewhere.

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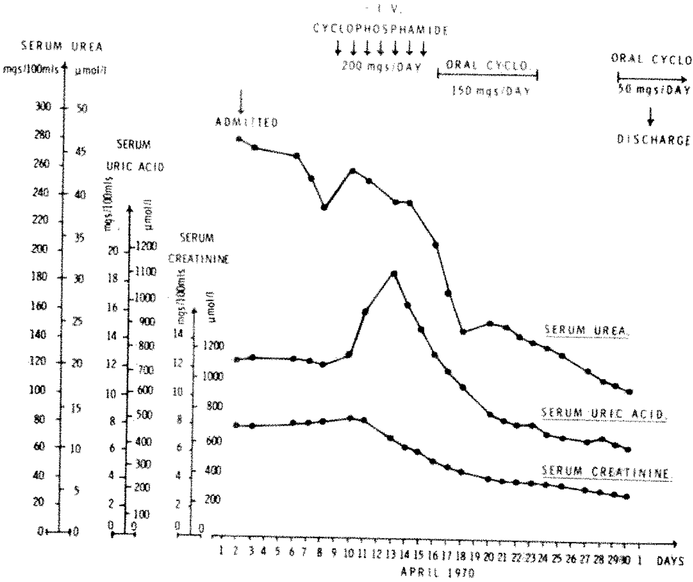

Fig. Blood nitrogen concentrations during admission. CYCLO = (cyclophosphamide).

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Antireflux Ureterocystostomy at the Vertex of the Bladder

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Among the many antireflux operative procedures, the antireflux ureterocystostomy at the vertex of the urinary bladder is a relatively unknown and rarely performed procedure. It is mentioned by Röhl and Ziegler (1969) as a procedure recommended for renal transplantation.

This is our first report on our results and experience with this kind of ureterocystostomy that we have adopted as our regular procedure for the repair of vesicoureteral reflux.

Materials and Methods

During the last 3 years 90 children were operated upon, 16 of them bilaterally, so that a total of 106 ureterocystostomies at the vertex were performed. 81 ureterocystostomies were made for the correction of vesico-ureteral reflux, 12 because of stenosis of the distal part of the ureter, 6 because of recurrent reflux and 7 as a correction of postoperative stenosis (Table I). All our cases were classified into one of 4 grades according to the degree of dilatation of the ureters and pyelon (Bridge and Roe, 1969). Most of the children (69) were in grade 3, 32 were in grade 4 and only 5 belonged to grade 2 (Table II). In 40 children in addition to the ureterocystostomy at the vertex, a remodelling of the ureter was performed.

The purpose of our antireflux ureterocystostomy at the vertex was to ensure a good flow of the urine into the bladder without development of stenosis and without recurrence of the reflux. The ratio between the length of the submucosal course of the ureter and its diameter was from 5 : 1 up to 8 : 1 in the empty bladder. Besides the submucosal course of the ureter, the angulation between the intravesical and extravesical course of the ureter during the act of micturition has an additional protective effect against the appearance of vesico-ureteral reflux (Fig. 1). Moreover, the ureteral orifice at the top of the bladder, when the child lies supine is on its highest point—preventing thus the appearance of a passive vesico-ureteral reflux.

Operative Technique

A catheter is placed into the bladder preoperatively. After a transverse suprainguinal incision in the lower abdominal skin crease, on the side of the reflux, a longitudinal pararectal dissection of the abdominal musculature is performed. The epigastric vessels are ligated, the processus vaginalis peritonei cut and the peritoneum pushed medially. After ligation of the umbilical vessels, the ureter is dissected carefully and cut in its intravesical part. The bladder is moderately distended with isotonic saline. On the vertex of the bladder, a little laterally, but not on the lateral wall, an incision of the vesical musculature down to the mucosa is made in the direction from the symphysis backwards and a little laterally. It is particularly important to undermine the musculature of the detrusor along both sides of the incision (Fig. 2). The bladder is then emptied through the indwelling catheter. An opening 0·5 cm wide is made through the mucosa close to the anterior margin of the incision, and 3 to 4 interrupted sutures with atraumatic catgut 4/0 are placed in the posterior wall of the ureter and in the opening in the vesical mucosa (Fig. 3). Before suturing the anterior wall of the ureterovesical anastomosis, a polyethylene tube is placed into the ureter through the abdominal wall, the bladder and the new anastomosis. The ureter is fixed to the

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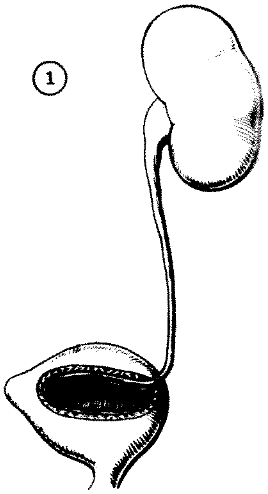

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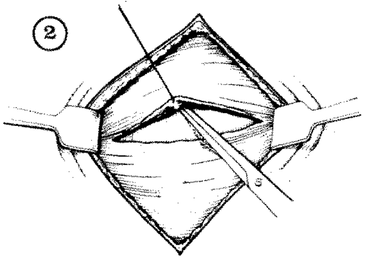

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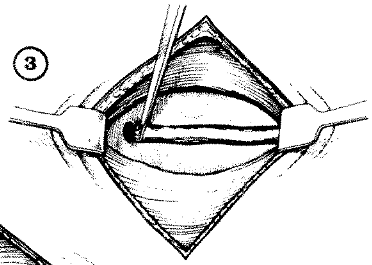

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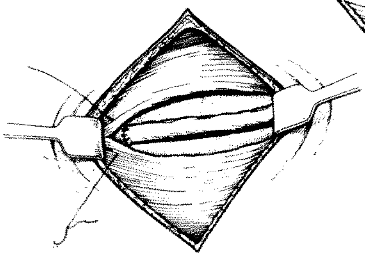

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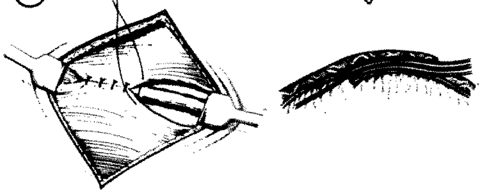

Fig. 1. Antireflux ureterocystostomy at the vertex includes the 3 antireflux mechanisms: (a) The submucosal course of the ureter is always long enough; (b) During the act of micturition there is an angulation between the intravesical and extravesical course of the ureter; (c) The ureteral orifice at the top of the bladder is on its highest point, when the child lies supine.

Fig. 2. The musculature of the detrusor must be undermined along both sides of the incision.

Fig. 3. 3 to 4 interrupted sutures are placed in the posterior wall of the ureter and in the orifice of the vesical mucosa.

Fig. 4. The ureter is fixed on the detrusor of the bladder with a U-shaped suture.

Fig. 5. The detrusor of the bladder and its adventitia is sutured over the ureter.

detrusor of the bladder close to the anastomosis with a U-shaped atraumatic chromic catgut 3/0 suture (Fig. 4). The detrusor of the bladder and its adventitia are then sutured over the ureter with interrupted stitches (Fig. 5). A 0 suction drain is placed into the paravesical space, and the abdominal wall is closed in the usual way.

The drain is removed on the 2nd postoperative day, the ureteral splint on the 6th or 7th day and the vesical catheter on the following day.

Results

Immediate postoperative complications were not seen. Postoperative urologic follow-up examinations were performed 3, 6, 12 and 24 months after the operation (Table III). In 6 children (5·7%), a postoperative reflux was found, but no postoperative stenosis was noted in any child. 4 of the 6 children with postoperative reflux belonged to the group of 13 children in which the antireflux plastic procedure by the Leadbetter-Politano technique had been previously performed. Thus, in this group of 13 children, the rate of operative failure was 30%. Excluding these 13 children, among the 93 ureterocystostomies in the vertex, without any previous operative procedure, the rate of postoperative reflux was 2·1% only (Table IV). In all cases and particularly

Table I

Ureterocystostomies at the Vertex

	Number of Cases
1. Vesicoureteral reflux	81
2. Stenosis of the distal ureter	12
3. Postoperative/recurrent/reflux	6
4. Postoperative stenosis	7
Total	106

Table II

Degree of Ureterectasis by Cystogram

Grade	1	2	3	4
Percentage of cases	0	4·7	65·1	30·2

Table III

Percentage of Cases in whom Postoperative Control are Performed.

3 months after operation	21%
3+6 months after operation	22%
3+6+12 months after operation	19%
3+6+12+24 months after operation	38%
	100%

Table IV

Results—Antireflux Ureterocystostomy (u-c) in the vault

	Number of Plastic Proced.	Postop. Stenosis	Postop. Reflux	Bacteriuria
1. Antireflux u-a in the vault (primary operation)	93	0	2/2·1%	1/1·0%
2. Antireflux u-c in the vault (second operation—after Leadbetter and Politano)	13	0	4/30%	2/15·4%
Total	106	0	6/5·7%	3/2·8%

in cases with grade 4 dilatation of the ureter, a marked regression of the dilatation was noted (Figs. 6, 7 and 8). In all the children the urine was sterile on culture, at the first postoperative follow-up examination, except in 3 cases with postoperative reflux.

Discussion

Whereas most of the antireflux procedures performed in cases of moderately dilated ureters are giving more or less satisfactory results, the most successful operation nowadays—that of Leadbetter and Politano—is not satisfactory in cases of severely dilated ureters. Williams and Eckstein (1965)

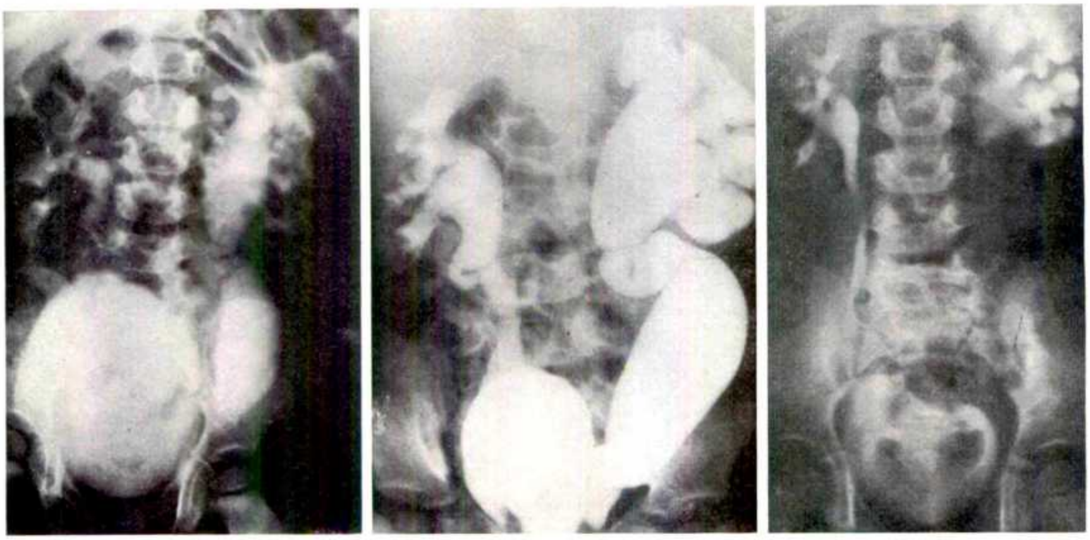

Fig. 6(a) 3-year-old girl. Intravenous urography (No. 373) shows poor bilateral renal function and marked dilatation of the left pelvicalyceal system and ureter. (b) The same girl. Voiding cysto-urethrogram (No. 373). Vesico-ureteral reflux grade 4 on the left side and grade 3/4 on the right side. (c) The same girl. Intravenous urography (No. 373) 2 years after bilateral antireflux plasty with bilateral ureteral tailoring, shows marked improvement. No signs of reflux on the voiding cysto-urethrogram.

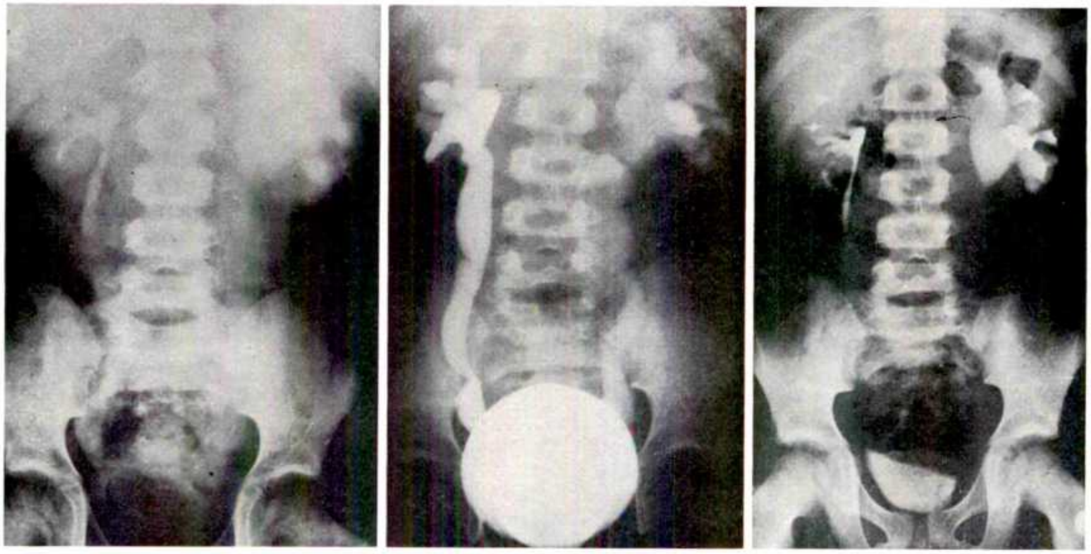

Fig. 7(a) 5-year-old boy. Intravenous urography (No. 76) shows poor bilateral renal function and marked dilatation of both pelvocalyceal systems, especially on the left side. (b) The same boy. Voiding cysto-urethrogram (No. 76). Vesico-ureteral reflux grade 4 on the left side and grade 3/4 on the right side. (c) The same boy. Intravenous urography (No. 76) after bilateral antireflux plasty with bilateral ureteral tailoring. Marked bilateral improvement. No reflux on the voiding cysto-urethrogram.

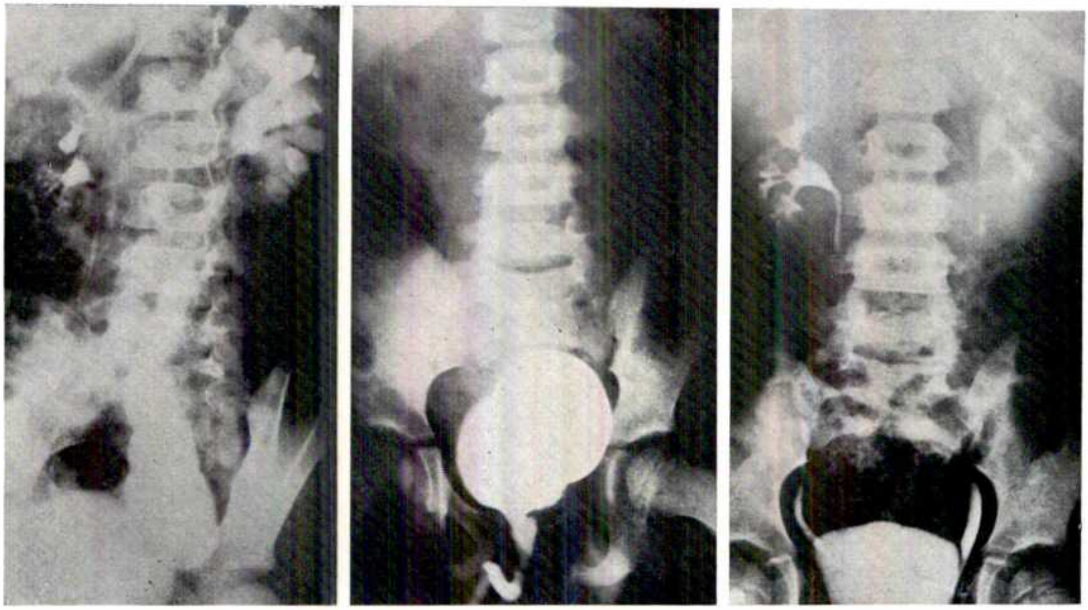

Fig. 8(a) 6-year old-boy. Intravenous urography (No. 74) shows enormous dilatation of the lower part and a little less dilatation of the upper part of the left ureter, caused by the intramural stenosis of that ureter. (b) The same boy. Voiding cysto-urethrogram (No. 74). The left bladder contour shows a large diverticulum. (c) The same boy. Intravenous urography (No. 74) 3 years after extravesical diverticulectomy and tailoring of the left ureter and antireflux plasty shows normal findings. No reflux on the voiding cysto-urethrogram.

were successful in only 37% of such cases. In our series of patients with grades 3 and 4 ureteral dilatation, the antireflux operations, according to Bischoff, Paquin, Williams, Leadbetter and Politano, were unsuccessful because of postoperative stenosis or postoperative recurrence of reflux on average in 47% of cases (Bradic *et al.*, 1973).

We believe that the fundamental cause of failure of all these procedures must be sought in the faulty location of the ureterocystostomy. All these operations attempt to reimplant the ureter in the region of the trigonum. Through the analysis of our own cases, we came to the conclusion that the submucosal course of the ureter after these procedures was never long enough to ensure a satisfactory antireflux mechanism, even when the ureter was tailored.

The most important prerequisite for the success of any antireflux operation is a long enough submucosal course of the ureter. The principal advantage of our ureterocystostomy at the vertex of the bladder is the almost unlimited possibility of creating a long enough submucosal course for reimplanted ureter. An exception are cases in which the ureter has already been shortened by a previously performed antireflux operation (Leadbetter and Politano). It is of the utmost importance in our operation to maintain the submucosal course of the ureter exactly as long as the incision of the detrusor. There is the danger that after the anastomosis of the ureter and the mucosal opening is made, a short ureter retracts, so shortening its submucosal course. This can be prevented by the U-shaped suture securing the ureter on the anterior margin of the incision of the detrusor. Furthermore, the submucosal tunnel for the ureter must be large enough, and its muscular lining strong enough. Therefore one has to mobilise the undercut margins of incision of the detrusor, being careful that the sutured margins are approximated accurately thus keeping the subsequent scar as small as possible. The submucosal course of the ureter at the vertex of the bladder becomes shorter after voiding, but it remains, nevertheless, long enough to prevent the appearance of reflux. This antireflux mechanism is supported by the angulation of the ureter at the new hiatus.

For the success of all antireflux operations it is very important to pay attention to the width of the ureter. We have always performed a reconstruction of the distal part of the ureter if it was 50% wider than normal, and if its wall was thickened. We believe that the importance of "tailoring" the ureter is not only in the narrowing of its lumen but also the resection of its circular musculature, which maintains its cylindrical shape.

Summary

This is the first report on the technique and the results of an antireflux ureterocystostomy in the vault of the bladder.

During the last 3 years, a total of 106 antireflux ureterocystostomies at the vertex of the urinary bladder has been performed.

In 93 cases without another preceding antireflux operation, only 2 (2·1%) recurrent refluxes were found, whereas in 13 cases where an antireflux operation had been performed previously, 4 cases of recurrent reflux were seen, making a 30% rate of operative failure in this particular group. In all other cases the end result was excellent; the urine has become negative on culture and the dilatation of the ureter has subsided.

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Ureteric Obstruction due to Uterine Prolapse

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Introduction

It does not appear to be widely known that uterine prolapse can cause ureteric obstruction with hydro-ureter and hydronephrosis. Few standard textbooks mention it (Jeffcoate, 1967) and the literature over the last 20 years reveals only occasional case reports (Levallois *et al.*, 1962; Deburge and Xerri, 1969; Jeukenne, 1970). The condition has however been recognised for a long time. In 1824 Froriep noted damage of the urinary tract due to prolapse of the uterus and in 1846 Virchow found hydronephrosis and hydro-ureter at autopsy in patients dying with complete uterine prolapse.

The reported incidence of ureteric dilatation in prolapse has varied in different series from 25% to 80%, probably because of differences in the severity of the prolapses under review (Halban and Tandler, 1907; Brettauer and Rubin, 1923; Kretschmer and Kanter, 1937; Racker, 1952). The worse the prolapse, the more marked the ureteric obstruction; thus Klempner (1952) found ureteric dilatation and hydronephrosis in 1 out of 20 first-degree prolapses, in 6 of 23 second-degree prolapses and 10 out of 25 third-degree prolapses. Renal function was remarkably seldom damaged; out of all these 68 patients, only 1 had any impairment of renal function. The obstruction can, however, be so severe as to cause fatal uraemia (Frank, 1931; Wallingford, 1939).

Since the frequency of this cause of ureteric obstruction may not be widely appreciated it may be helpful to report 2 illustrative cases.

Case Reports

Case 1. Mrs M. D., aged 66, gave a 10-month history of prolapse with vaginal discharge and bleeding, episodes of haematuria and frequency of micturition. Shortly before admission the haematuria and frequency became worse and she had difficulty in starting to void.

On examination she was unwell. There was no sign of bladder distension. She had an enormous procidentia. The urine contained numerous red cells and occasional white cells. Culture gave a growth of *E. coli.*

On admission her blood urea was 335 mg/100 ml, electrolytes were normal. The urinary output in the final 24 hours was 1530 ml. Her fluid intake was limited, she was put on a low-protein diet and a ring pessary was inserted to control the procidentia. Following these measures her blood urea fell rapidly.

2 weeks after admission, an IVP showed bilateral hydro-ureters and hydronephrosis with a moderate post-micturition residue (Fig. 1a and b).

4 weeks after admission she had a vaginal hysterectomy and repair. 3 months after operation, IVP showed marked improvement, the previous bilateral hydro-ureter and hydronephrosis having virtually returned to normal apart from some slight dilatation and tortuosity of the left ureter. Her blood urea was 54 mg/100 ml.

Case 2. Mrs A. A., aged 62, gave an 8-year history of prolapse. 3 months previously she had felt generally unwell with backache, haematuria and frequency; this cleared up but was followed by a further similar episode. 3 weeks before admission her "womb came down" and she stated that later on in the day she had to strain to pass urine, though first thing in the morning she was able to pass urine normally.

On examination she had a marked procidentia and was slightly tender in the right loin. The urine was clear.

Her blood urea was 30 mg/100 ml, electrolytes were normal. An IVP showed a dilated right upper tract and a normal left side (Fig. 2, A and B). The bladder was small and somewhat deformed on the right. Cystoscopy showed an oedematous trabeculated bladder and a ureterogram showed a dilated right ureter.

12 days after admission a vaginal hysterectomy was performed with an anterior and posterior repair.

17 days after operation an IVP still showed some right hydronephrosis, but the right ureter was almost normal in calibre (Fig. 3).

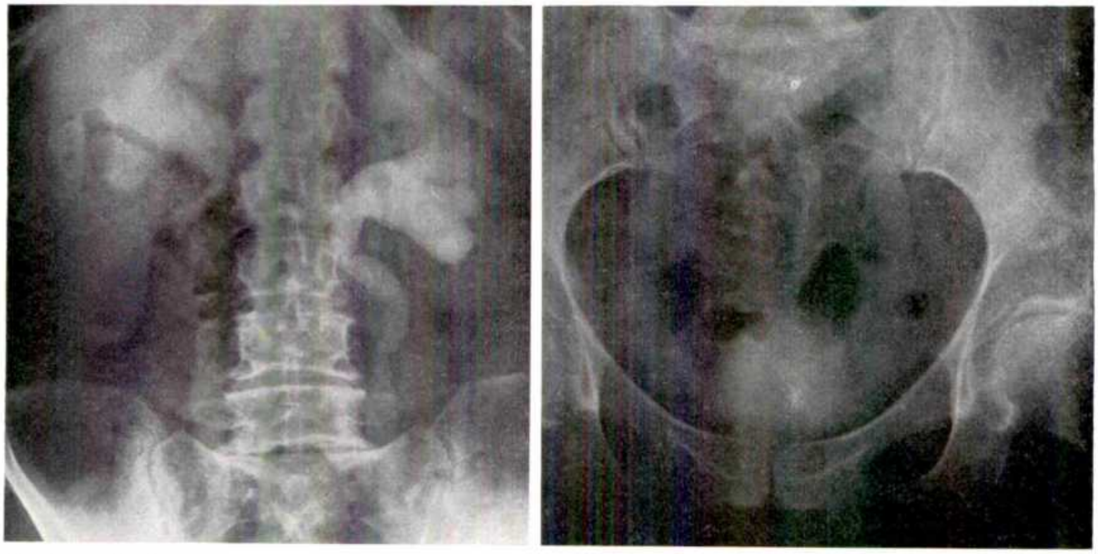

Fig. 1 a and b. Case 1. IVP showing bilateral hydro-ureters and hydronephrosis with moderate post-micturition residue.

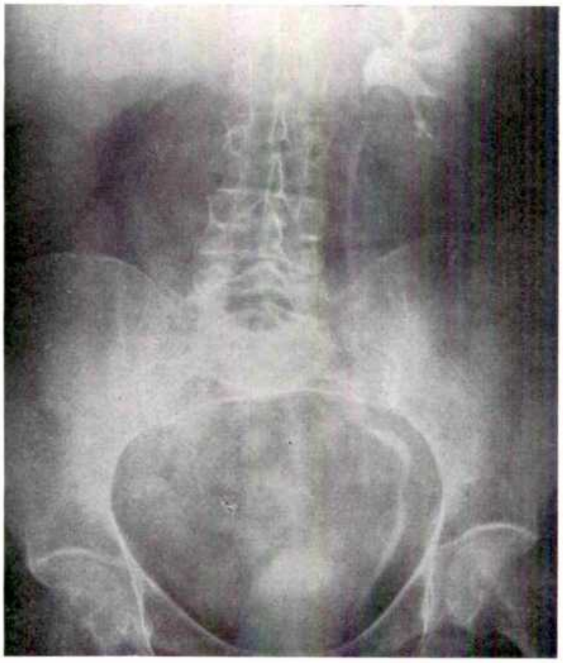

Fig. 2. Case 2. IVP showing a dilated right upper tract and a normal left side.

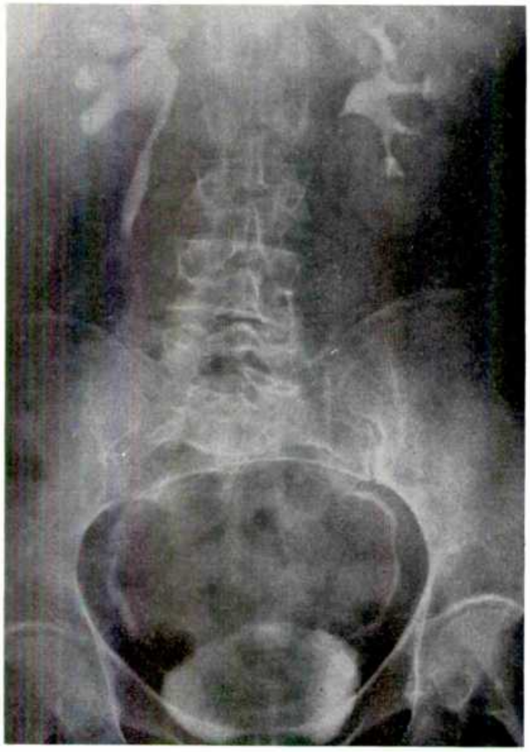

Fig. 3. Case 2. IVP 17 days after hysterectomy and repair.

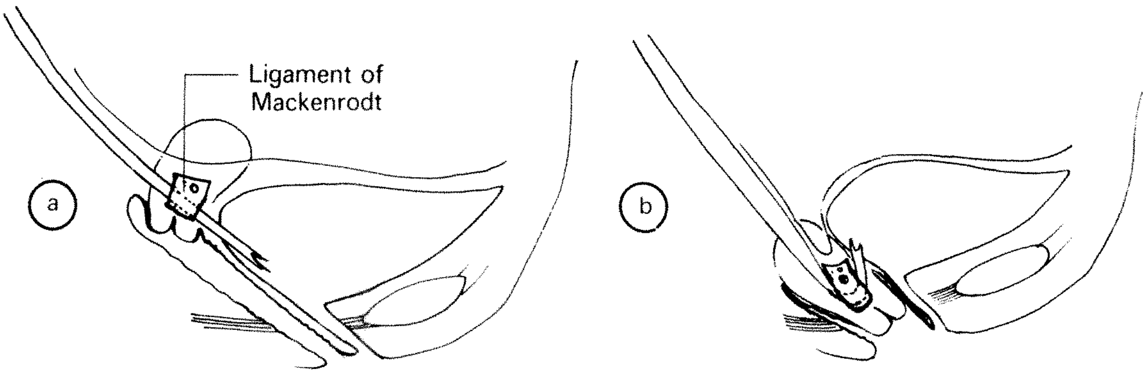

Fig. 4(a) Diagram to show the ligaments of Mackenrodt and their normal relationship to the ureters. **(b)** Diagram to show the ligaments of Mackenrodt pulling down and kinking the ureters as the uterus descends.

Comment

Even though uterine prolapse is so common, and a degree of obstruction to the ureter seems to occur relatively often, it is not at all obvious why the ureter becomes obstructed. It cannot be narrowed by being stretched in the wall of the bladder, since the junction between the narrow part and the dilated part of the ureter is found some 2 to 3 cm from the wall of the bladder, as occurred in the 2 cases reported here, and it is not due to urethral obstruction by kinking of the urethra, since there is seldom much residual urine (Brettauer and Rubin, 1923). It has been suggested that as the uterus and bladder descend through the genital hiatus in the levator sling, the ureters are compressed against the edge of levator ani (Halban and Tandler, 1907). Brettauer and Rubin (1923) and Wallingford (1939) thought that the obstruction was caused by the uterine vessels which form a sling as they are pulled over the ureter as the uterus descends. It seems more likely, however, that as the uterus descends, the lateral cervical ligaments of Mackenrodt pull down upon and kink the ureters which run through them (Fig. 4a and b). If the ureters are catheterised it can be shown that traction on the cervix will kink them (Lieberthal and Frankenthal, 1941). The drag on the ureters pulls on the interureteric bar and raises it to form a ridge (Roberts, 1953).

Whatever the exact mechanism by which these ureters are obstructed in association with prolapse, it is evident from the experience reported here and in the literature that the obstruction is readily corrected by correction of the uterine prolapse, either by means of a pessary, or an operative repair (Klempner, 1952).

Summary

2 cases of ureteric obstruction due to uterine prolapse are reported, one of whom was uraemic. Both were cured by repair of the prolapse.

I am very grateful to Professor J. P. Blandy for his helpful advice and encouragement and to Mr J. C. Hartgill and Mr J. Suchet for permission to report these cases.

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Bilateral Vesico-ureteral Reflux with Pyelonephritis in Identical Twins

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Since recognising the importance of persistent primary vesico-ureteral reflux in recurrent urinary tract infections much has been written about the embryology, anatomy and function of the vesico-ureteral junction (Hutch, 1961; Tanagho and Hutch, 1965; Feins *et al.*, 1971). Very little attention was given to the possibility that this defect may be, in some cases, a familial hereditary lesion (Tobenkin, 1964; Baker *et al.*, 1965).)

Until 1973 only 52 families with more than 1 sibling suffering from reflux were reported in the English literature (Stephens and Lenaghan, 1962; Tobenkin, 1964; Baker *et al.*, 1965; Ambrose, 1969; Mulcahy *et al.*, 1970; Burger and Smith, 1971; Amar, 1972; Schmidt *et al.*, 1972; Miller and Caspari, 1972). Among them we were able to find only 3 reports of vesico-ureteral reflux occurring in identical twins (Stephens, Joske and Simmons, 1955; Mebust and Foret, 1972; Pochaczevsky, Naysan and Ratner, 1974). To support the possibility that primary vesico-ureteral reflux is a familial disease we will report a 4th set of identical twins with vesico-ureteral reflux and bilateral pyelonephritis.

Case Report

The patients were identical twins, Caucasians, aged 20. The first brother (R. F.) was admitted as an emergency, with left ureterolithiasis. He had no history of urinary infections or any other urinary complaints. In the excretory urogram (IVP), a stone obstructing the upper 1/3 of the left ureter was seen, with proximal hydronephrosis. On the right side there were pyelonephritic changes. The size of the kidney was normal but the parenchyma was thin.

Voiding cysto-urethrogram demonstrated a marked low pressure vesico-ureteral reflux on the right side and a mild high-pressure reflux on the left side. Ureterolithotomy on the left side was performed with no complications. A month later a Lich-Gregoir antireflux operation was performed on the right ureter. Renal function tests were within normal limits.

The patient was asked to send his identical twin brother (D. F.) for examination. Although he had no history of urinary infections, a full urological investigation was made. Severe bilateral pyelonephritic changes were found with marked bilateral low-pressure reflux to the kidneys. Kidney function tests were within normal limits. A bilateral Lich-Gregoir anti-reflux operation was successfully performed.

Discussion

Most investigators agree that vesico-ureteral reflux is not a normal finding. The pathogenesis of primary reflux is controversial. The observation that there is a relative infrequency of reflux among black Americans (Waterhouse, 1967; Schmidt *et al.*, 1972) suggests that genetic factors play an important role in this lesion, as in many other urological abnormalities. Occurrence of vesico-ureteral reflux among members of the same family is evidence that ureterovesical incompetence is an inherited defect. Our report and the other 3 reports (Stephens *et al.*, 1955; Mebust and Foret, 1972; Pochaczevsky *et al.*, 1974) of identical twins with this anomaly firmly support this theory.

The mode of inheritance is not clear. There are many reasons for it. Not all those with reflux are symptomatic and when they are there is a wide range of severity. In some, the first symptoms are of terminal pyelonephritis with renal failure.

In some cases reflux is caused or enhanced by other malformations, like double ureters or ureterocele (Amar, 1968). The fact that the incidence of primary reflux decreases as one passes from childhood to maturity makes the evaluation of the mode of inheritance more difficult (King, 1972). Thus there is a possibility that a parent without reflux had reflux in childhood and had inherited it.

At present there are two hypotheses to explain the mode of inheritance. Miller believes that it is transmitted by a dominant gene with incomplete penetrance (Miller and Caspari, 1972). On the other hand, Burger states that it is transmitted by multiple genes of cumulative effect with a critical threshold for the manifestation of reflux (Burger, 1972).

Although the mode of inheritance is not agreed upon, the over 50 families with a "familial trait" of vesico-ureteral reflux merits attention. When an individual is affected his close relatives should be carefully examined and when there is a possibility of reflux a full investigation should be performed. We believe that in all cases of identical twins the two should be thoroughly investigated. We have not found a report of twins examined, where only one of them was affected.

Early recognition of vesico-ureteral incompetence in other members of the family is important, as we are dealing, in most instances, with a curable disease that at times runs a silent though destructive course.

Summary

A case of identical twins with bilateral vesico-ureteral reflux is presented.

This case supports the hypothesis that primary vesico-ureteral incompetence may be an inherited lesion.

The importance of investigating close relatives, especially identical twins, is stressed.

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Short Case Report

Multiple Ureteral Diverticula Associated with Bilateral Ureterocoeles

A male of 67 presented with a 4-month history of intermittent burning left-sided loin pain, which radiated to the scrotum. There was no nausea, vomiting or haematuria. Physical examination was negative.

Urinalysis revealed moderate albuminuria, pus cells and a scanty growth of gram-negative bacilli.

Abdominal X-rays were normal. Excretion urography demonstrated normal renal anatomy. However, numerous small diverticula were noted along both ureters (Fig. 1). Furthermore, the typical "cobra-head" appearance of a ureterocoele was present on the left (Fig. 2). A smaller right-sided ureterocoele was also seen. Frank hydronephrosis was absent, but evidence of some pelvi-ureteric stasis was present. No diverticula were present on barium enema.

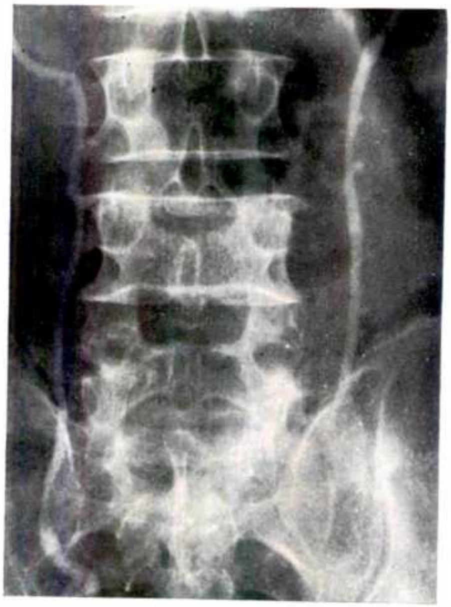

Fig. 1

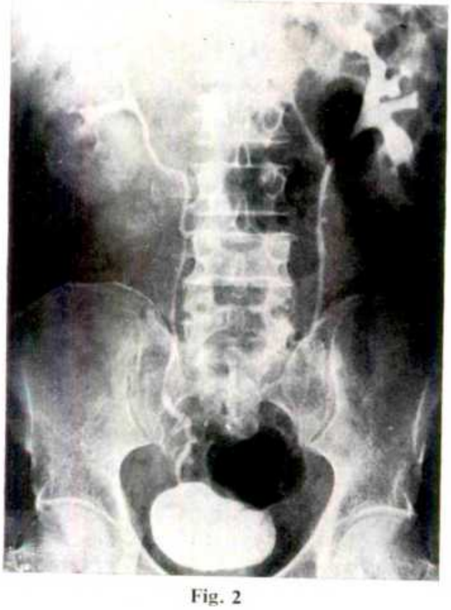

Fig. 2

Comment

Multiple ureteric diverticula are rare. The association of bilateral ureterocoeles has not been previously described.

Urinary tract infection, calculi or prostatic hypertrophy have, commonly, been associated features in the reported cases of multiple ureteric diverticula (Khonsari and Oliver, 1971). In this case the presence of infection and some ureteric stasis, both of which are also recognised complications of ureterocoele (Thompson and Kelalis, 1964), is further evidence of their aetiological importance.

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The Effect of Chlorhexidine Irrigation of the Bladder in the Rat

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The instillation of an aqueous solution of chlorhexidine into the bladder at the end of catheterisation has been shown to reduce the incidence of infection associated with this procedure (Paterson, Barr and MacDonald, 1960; Gillespie *et al.*, 1962). However, haematuria has been reported in some patients after the frequent use of aqueous solutions of chlorhexidine digluconate 1 : 5,000 (McFadyen and Simmons, 1968; Pearman, 1971) or chlorhexidine diacetate 1 : 5,000 prepared from the concentrate (Paterson *et al.*, 1960). It was therefore decided to study the effect of chlorhexidine irrigation of the rat bladder using the digluconate salt which is the form recommended for irrigation of the human bladder (Rubbo and Gardner, 1965; *British Pharmacopoeia*, 1973).

Materials and Methods

Insertion of Catheter into Rat's Bladder. 3-month-old Wistar male rats were anaesthetised with 22·5 mg of thiopentone in 0·5 ml of sterile distilled water injected intraperitoneally. The abdomen was surgically prepared by using 2·5% hexachlorophane soap which was rinsed with water and subsequently swabbed with 70% alcohol. A midline incision was made to expose the fundus of the bladder. The proximal attachment of a sterile Intracath ® (Deseret Pharmaceutical Co., Sandy, Utah, USA, Cat. No. 3132) was cut to form a small cuff. This cuff was inserted into the bladder and held in position with catgut sutures. The free end of the catheter was passed through a needle which was so positioned that the catheter emerged through the skin at the base of the tail, thereby preventing the animal from damaging the catheter when it was held in a cage with its tail protruding. The needle was removed and the wound closed in layers. A syringe containing 30 ml of an aqueous solution of chlorhexidine digluconate was attached to the catheter and the injection controlled by a Sage Pump (Cat. No. 355) set at 52·6/and Range × 1/1,000 which gave a flow rate of 1·5 ml per hour. The rats were sacrificed at predetermined times and the bladder was removed immediately and fixed in 10% formol-saline with 0·3 ml of the fixative also being injected through the catheter. The bladders were then bisected longitudinally and 5μ paraffin embedded. H. & E stained sections were examined from both halves.

Preliminary Experiments. A series of preliminary experiments were done to gain experience so that a test series of experiments with controls could be performed with a blind assessment of the results. In the first experiments 11 rat bladders were irrigated with chlorhexidine digluconate in strengths of 1/5,000, 1/10,000, 1/20,000 for periods of 20 to 48 hours. As a control 9 rat bladders were irrigated with saline for periods of 1½ to 48 hours.

Results

In all bladders the mucosa around the catheter cuff was flattened or eroded with varying degrees of acute inflammation. In the serosa around the sutures holding the catheter in place there were also degrees of acute inflammation, haemorrhage, oedema and fibroblastic proliferation. In most instances these inflammatory and reparative changes were localised to the area of surgical trauma, but in some of the 48-hour experiments, the inflammatory changes had spread in the serosa of the bladders but spared the mucosa. The extent of the surgically induced inflammation was also dependent on the position of the catheter. If properly aligned then the mucosal changes only occurred in those areas about the shoulders of the cuff of the catheter. If, however, the

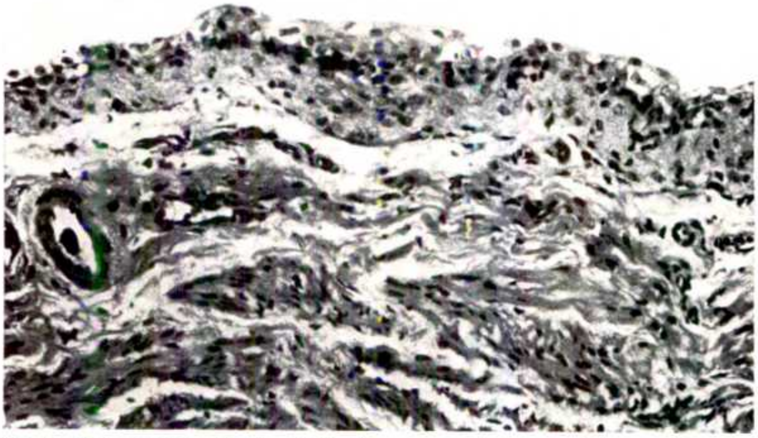

Fig. 1. Photomicrograph of rat bladder mucosa showing cellular swelling and vacuolation and scored as mild change. H & E. × 180.

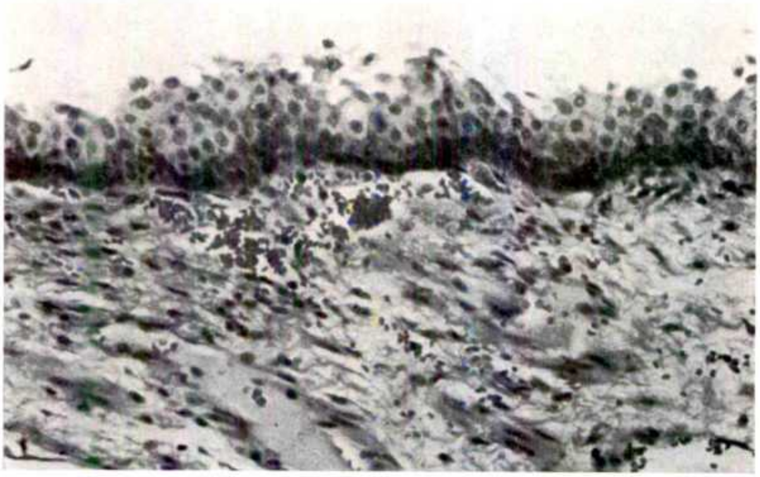

Fig. 2. Photomicrograph of rat bladder mucosa showing proliferation, superficial desquamation, fibroblastic proliferation and slight inflammatory cell infiltration in the lamina propria. Scored as moderate change. H & E. × 180.

catheter was skewed then the mucosa opposite the face of the cuff was also involved. This did not necessarily provide difficulties in interpretation as the rat bladders were about 1·2 cm in length and even with badly skewed catheters there was usually 0·6 cm of non-traumatised mucosa to assess.

Chlorhexidine Digluconate Irrigated Bladders. The mucosal changes ranged from increased cellular basophilia, nuclear anisocytosis, frequent mitoses, individual cell degeneration, focal proliferation to focal or widespread erosive inflammation with haemorrhage.

Saline Irrigated Bladders. The mucosal changes were mild in 7 cases and consisted of slight epithelial flattening, squamoid change, swelling, individual cell karyolysis, cytoplasmic vacuolar

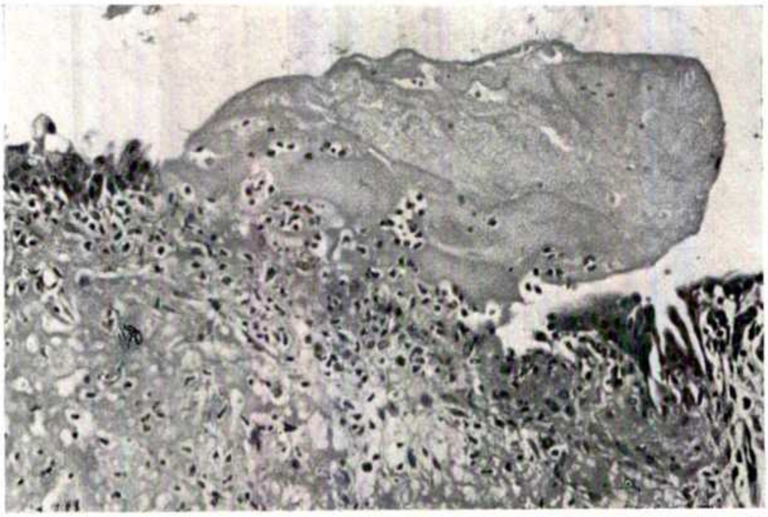

Fig. 3. Photomicrograph of rat bladder mucosa showing florid erosive cystitis with haemorrhage. Scored as severe change. H & E. × 180.

change and a submucosal oedema. 2 bladders, however, showed florid cystitis. One of these contained many bacteria in the inflammatory areas and was therefore considered to be an infective cystitis. The other was a 48-hour experiment in which the perfusion apparatus failed at 24 hours.

These preliminary observations indicated that chlorhexidine irrigation of the rat bladder caused irritation of the mucosa leading to erosive cystitis with haemorrhage. To test the validity of these findings a series of experiments were performed with blind assessment of the results.

Test Series of Experiments

41 rat bladders were irrigated with either saline or chlorhexidine (1 : 5,000 or 1 : 10,000) by W. H. The period of time of irrigation was intended to be 48 hours but if the animal's condition deteriorated or it appeared to be suffering, then the experiment was terminated. 26 bladders were irrigated for 48 hours, 5 for 20 to 24 hours and 10 for 6 to 14 hours. At the end of the experiment the animals were killed instantaneously by a blow on the head and the bladders injected with 0·3 ml of buffered 10% formol-saline. The bladders were then removed, placed in buffered 10% formol-saline, numbered in numerical order and sent to L. R. M. for examination. The bladder changes were graded into 1 of the following 3 categories:

1. Mild changes—epithelial flattening, focal superficial desquamation, cytoplasmic vacuolation, occasional mitosis, sub-mucosal oedema (Fig. 1).
2. Moderate changes—cellular basophilia, frequent mitoses, cellular proliferation, focal areas of mucosal desquamation, cellular swelling, with fibroblastic proliferation or mild acute inflammatory cell infiltration in the lamina propria (Fig. 2).
3. Severe changes—mucosal erosion, inflammatory cell infiltration, fibrin precipitation, haemorrhage (Fig. 3).

Results

Table I shows the numbers of bladders with mild, moderate or severe changes and the associated irrigating fluid. The chi-squared test applied to either the figures as given or to the combined results of chlorhexidine 1 : 5,000 and 1 : 10,000 give results of 17·0 and 16·36 and are of a high

Table I

Results of Blind Assessment

Irrigating Fluid	Bladder Changes			Totals
	Mild	Moderate	Severe	
Chlorhexidine 1 : 5,000	2	4	12	18
Chlorhexidine 1 : 10,000	...	3	6	9
Total	2	7	18	27
Saline	9	3	2	14

degree of statistical significance. The conclusion therefore is that rat bladders irrigated with either chlorhexidine 1 : 5,000 or 1 : 10,000 for periods of 6 to 48 hours develop erosive inflammation in a high proportion of cases.

Discussion

Chlorhexidine is extensively used in medical practice as an antiseptic. It is effective against a wide range of bacteria (Davies *et al.*, 1954) and only occasional reports of the development of bacterial resistance have appeared (Gillespie *et al.*, 1967; Stickler, 1974). Its effect on mucosal surfaces had seemed inconsequential (Beeuwkes and de Vries, 1956), but Calman and Murray (1956) although stating that no cases of irritation had occurred amongst 10,000 patients warned about chlorhexidine solution stronger than 1 : 10,000 for use on delicate mucous membrane. Caldwell (1970) claimed that the use of toothpastes or mouth washes containing chlorhexidine softened the oral epithelium and both contributed to the formation of aphthous ulcers as well as retarded healing if the pastes or mouth washes continued to be used. The reports by Paterson *et al.* (1960), McFadyen and Simmons (1968) and Pearman (1971) of haematuria after instillation of chlorhexidine diacetate or digluconate into the bladder suggested severe irritation of the bladder mucosa. This hypothesis has now been confirmed in rat bladder mucosa where irrigations of chlorhexidine digluconate 1 : 5,000 and 1 : 10,000 for periods of 6 to 48 hours produced erosive cystitis in a high percentage of cases. Chlorhexidine digluconate cannot therefore be recommended as the antiseptic of choice for procedures involving frequent and prolonged contact with mucosa. This is not to say that chlorhexidine should not be used as an urologic irrigating fluid as many procedures are brief and non-repetitive, unlike frequent intermittent catheterisation for several weeks following acute spinal cord trauma.

The observations by Paterson *et al.* (1960) that haematuria did not occur in the clinical situation if the additives in chlorhexidine diacetate concentrate were removed led them to postulate that the wetting agent (Lissapol NX) was responsible for haematuria. The chlorhexidine digluconate used in our experiments was prepared from a sterile pure 20% solution and the irritant effects can therefore only be ascribed to the digluconate form of the antiseptic itself.

The mucosolytic action of chlorhexidine in these experiments may be related to its bacterial action. This action is believed to be due to the lipophilic groups in the chlorhexidine molecule which causes a disorientation of the cell's lipoprotein membrane, thereby rendering the osmotic barrier ineffective and altering membrane permeability (Hugo and Longworth, 1964, 1965). Hicks (1966) showed that the permeability of rat bladder mucosa depended on the integrity of lipoprotein cell membrane as well as the presence of disulphide bridges located in keratin in the thick asymmetric membrane which limits the luminal face of the superficial cell. Chlorhexidine damage to rat bladder mucosa is very likely an osmotic injury, secondary to an alteration in the integrity of lipoprotein membranes. This type of injury has been suggested as part of the mechanism of cyclophosphamide-induced sterile haemorrhagic cystitis (Schultz and Weldon, 1974).

Summary

Rats' bladders were irrigated with aqueous solutions of chlorhexidine digluconate 1 : 5,000 or 1 : 10,000 for varying periods up to 48 hours. Histologic examination of the bladders showed severe erosive cystitis in a high percentage of cases.

It is concluded that chlorhexidine cannot be recommended for prolonged irrigation of the bladder or for instillation during intermittent catheterisation where chlorhexidine has repeated and prolonged contact with bladder mucosa.

We thank Mr R. J. Oakeshott, FRCS(Edin.), FRACS, for help and advice on surgical techniques, and Dr J. W. Pearman for his encouragement and interest. Dr J. R. Warren assisted with the statistical assessment. The photographs were prepared by the Department of Medical Illustrations, Royal Perth Hospital.

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Short Case Report

Appendico-vesico-colic Fistula

Vesico-intestinal fistulae, in most instances, are secondary to carcinoma or diverticular disease of the colon. It is rare for the appendix to be affected. This fistula, which involved the appendix, sigmoid colon and bladder, appears to be unique in the literature.

Case Report

A 55-year-old man was admitted with a 4-month history of frequency, burning passage of faecal material per urethram, and episodes of diarrhoea. For 35 years he had had episodes of frequency and burning of micturition at 2-yearly intervals.

His urine was infected with *E. coli* and a plain X-ray showed a left staghorn calculus. A barium enema was bizarre—the contrast medium rapidly entered the bladder and filled the caecum. The double fistula was confirmed by a micturating cystogram (Fig. 1).

At operation a communication was found between the appendix, bladder and sigmoid colon (Fig. 2). The sigmoid colon, apart from 2 small diverticula, and the bladder were otherwise normal. The appendix was grossly enlarged then filled. The 3 structures were separated, the appendix was removed, the bladder and sigmoid closed in layers with a tongue of omentum between the bladder and sigmoid colon and the colonic closure protected by a loop colostomy, which was closed 3 months later.

The appendix and wall of the fistula showed chronic inflammatory changes, and the fistula was lined by a well-developed colonic type epithelium, which suggested that the fistula had been long standing. There was no evidence of malignancy or granuloma formation.

Comment

A fistula between the intestinal tract and the bladder is uncommon and Lett in 1932 could only find 10 instances in 96,192 surgical admissions and were revised by Parton (1958).

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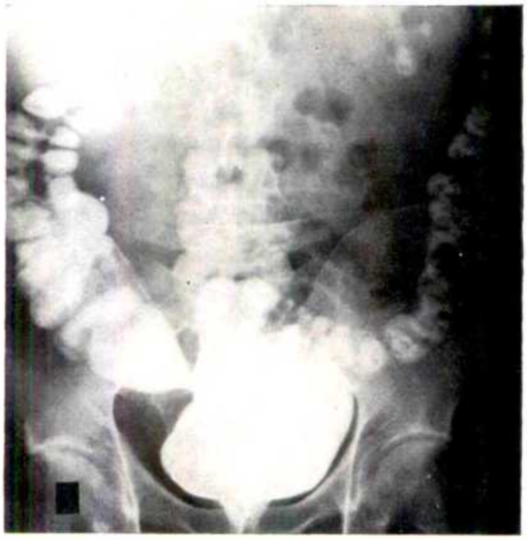

Fig. 1

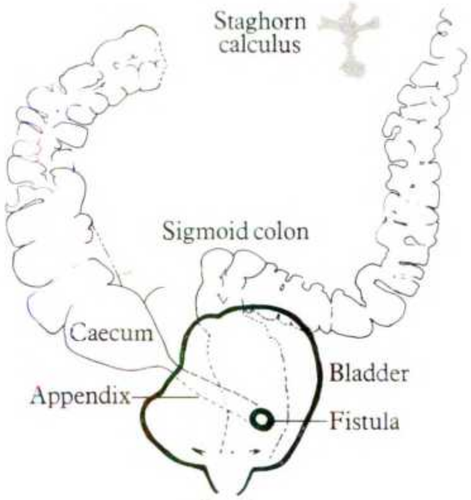

Fig. 2

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Urinary Infection and Prostatectomy

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Several methods of management have been advocated to reduce the incidence of urinary infection after prostatectomy. They include the prophylactic use of antibiotics (Plorde *et al.*, 1965), auto-irrigation diuretics (Essenhigh, Clayton and Taha, 1970), antimicrobial irrigation through indwelling urethral catheters (Mahoney and Persky, 1965) and "no catheter" surgical techniques (Debenham and Ward, 1960; Spencer, 1967; Cass, 1969); most surgeons now use closed catheter drainage with careful aseptic management. However, before accepting the virtues of a new method which might claim to reduce the incidence of urinary infection before and after prostatectomy, a base line should be available for comparison. The following retrospective study presents the incidence and nature of urinary infections in 140 consecutive patients with benign prostatic hypertrophy.

Patients and Methods

The patients were admitted either for elective operation after preliminary out-patient assessment or urgently, following retention of urine. Those patients with painful acute retention (61) or chronic retention (4) associated with uraemia (blood urea> 120 mg%) were managed first by urethral catheterisation and closed bladder drainage.

Catheterisation was carried out in the ward using an aseptic technique: mask, gown and gloves were worn, the glans penis was cleaned with 5% aqueous cetrimide, the urethra was anaesthetised and lubricated with 2% lignocaine gel, a Foley Simplastic catheter was passed and connected to an Aldon disposable drainage bag with non-return valve and dependent tap. Prostatectomy was carried out as soon as possible after full assessment. Auto-irrigation diuresis was induced in 42 patients with frusemide 40 mg i.v. at completion of prostatectomy. Postoperatively, the drainage system was not interrupted except to wash out clots which could not be milked down the catheter. Urine specimens for microscopy and bacteriological examination were taken twice weekly from the urine collection bags until the catheter was removed; thereafter, twice-weekly mid-stream specimens of urine were examined.

Infection was defined as bacteriuria of more than 100,000 colonies per ml on a single occasion but, unless there were clinical indications, antibacterial therapy was not instituted until the results of *in vitro* sensitivity testing became available.

Approximately 6 weeks after operation further urine specimens were obtained at the Urological Out-patient Clinic from patients who had had postoperative urinary infection.

Results

In 106 of the 140 patients the urine was sterile on admission to hospital but in 4 cases it subsequently became infected before prostatectomy was carried out: 2 occurred in 41 of the patients who required preliminary catheterisation but in 2 others catheters were not used.

In 34 patients the urine was infected on admission and in 24 of these indwelling catheters were required. The urines became sterile with appropriate antibiotic therapy before prostatectomy in 14 but in the remaining 20 the infection persisted for varying periods despite specific antibacterial treatment.

At the time of prostatectomy the urine was sterile in 116 patients but subsequently became infected in 37 and treatment with specific antibacterial agents was instituted in 27 of the 37 cases.

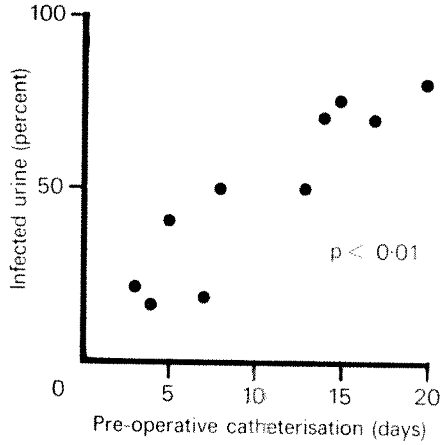

Fig. 1. The correlation between the incidence of preoperative urinary infection and the duration of preoperative catheter drainage is significant ($P < 0{\cdot}01$).

However, at the time of discharge from the wards the urine was sterile again in all 116 patients. In addition to this the urine in 10 of 24 patients with infection before prostatectomy was sterile after operation although in 4 cases 2 courses of anbibacterial therapy were required to treat recurrent infections identical to those present before operation. Thus, the urine was sterile in 126 of the 140 patients at the time of their discharge from the wards.

At follow-up, approximately 6 weeks after prostatectomy, there remained only 4 patients with persistent infection; of these, 2 had diabetes mellitus with an associated neurological abnormality of the bladder, 1 had cerebral atrophy and was incontinent before and after prostatectomy and 1 had endured an indwelling catheter for 18 months before operation and developed a posterior urethral stricture which required subsequent treatment.

Of 42 patients who received frusemide, 30 had sterile urine at operation; 6 of 30 (20%) developed infection postoperatively compared with 33% not so treated. In these patients infection developed between the 3rd and 14th postoperative day; however, all had sterile urine at the time of discharge. Of 12 patients whose urine was infected at operation 8 had sterile urine on discharge from the ward.

Statistical analysis failed to show any relation between the incidence of postoperative urinary infection and the type of prostatectomy. It occurred in 11 of 39 cases after T.U.R., 23 of 56 after retropubic and 24 of 43 after transvesical prostatectomy. However, the incidence of infection could be correlated with the duration of preoperative catheterisation (Fig. 1). The commonest organisms before and after prostatectomy were coliforms but there was a significant increase in the incidence of Proteus species after prostatectomy. Multiple organisms were found in 18 of 40 cases before operation but in only 8 of 37 after operation.

Discussion

Patients with prostatic obstruction may develop urinary infection before or after admission to hospital; when it develops in hospital it may either precede or follow catheterisation and/or prostatectomy. Infection before hospitalisation occurred in 24% (34 of 140) in the present series and this incidence compares favourably with that reported by MacDonald *et al.* (1957) in non-catheterised patients with benign prostatic hypertrophy.

Our patients lived in the metropolis and did not require domiciliary catheterisation; this may not always be the case and when patients live in rural areas, remote from hospitals with urological units, emergency catheterisation may have to be undertaken in unfavourable circumstances and may influence the incidence of subsequent urinary infection. Certainly, there was a positive correlation between the incidence of urinary infection and the duration of preoperative catheterisation in our own series of hospitalised patients (Fig. 1) and in the majority of our cases the

Table I

	Retropubic	Transvesical	Transurethral	Cryoprostatectomy
Total	56	43	39	2
Infected at operation	9	8	5	2
Infected before discharge	24	24	11	2
Infected 6 weeks postoperatively	2	1	1	0

Table II

Bacteriological Findings

	Pre-op	Post-op
Coliforms	28	32
Escherichia coli	11	5
Klebsiella species	6	8
Proteus species	5	12
Pseudomonas aeruginosa	6	7
Str. faecalis	12	9
Staph. aureus	2	9
Staph. albus	1	8
Others	5	4

catheterisation was carried out by trained members of the urological unit and proper facilities were available.

Antibacterial therapy did not eradicate infection in 59% of the 34 patients with infected urines before prostatectomy; indwelling catheters were required in 24 of the 34. After prostatectomy, infection developed in 37 of 116 (31%) and there was an increased incidence of Proteus species organisms. But in contrast with the results of antibacterial therapy before prostatectomy it was possible to sterilise the urine in all 37 cases after prostatic surgery, before the patients were discharged from hospital. Presumably reinstitution of natural micturition contributed to the difference. Only 10% of the 140 patients in the series had urinary infections when discharged from the urological ward to the out-patient clinic, an incidence comparable to that reported by Essenhigh *et al.* (1970), but significantly less than that reported by Bruce, Rao and Kennedy (1971). When the patients were reviewed 6 weeks after prostatectomy the infection rate was less than 3% (4 of 140) and there were pertinent reasons for the persistent infection in these exceptional cases. Although the figures were too small to be of statistical significance frusemide seemed to be effective in lowering the incidence of postoperative infection and when this did occur it developed late in the postoperative period. This suggests that prolonged diuresis after operation using this drug may be valuable.

The criterion of urinary infection in patients with prostatic obstruction varies in different reports: for example, Essenhigh *et al.* (1970) accepted colony counts of 10,000/ml, Genster and Madsen (1970) 5,000/ml and Miller *et al.* (1958) 3,000/ml in 2 consecutive specimens, while others (Marshall, 1967; and Williams, 1972) have not defined their criteria. We have used counts > 100,000/ml on a single occasion and examined the urine twice weekly. If this is not done it is possible to overlook infection and it follows that the incidence of infection will be artificially low. Infection after prostatectomy resolved spontaneously without any drug therapy, before the patients were discharged from hospital in 10 of 37 cases.

The incidence of postoperative infection is said to be low after transurethral prostatectomy: Symes *et al.* (1972) reported an incidence of 5% but Genster and Madsen (1970) found that 52% had bacteriuria. In our series there were 34 patients with sterile urine at the time of resection but infection subsequently occurred in 6 (18%). Repeated bi-weekly screening for bacteriuria need not be an extravagant investigation if a dip-slide technique is used (Jackaman, Darrell and Shackman, 1973), and this is recommended if the true incidence of urinary infection before and after prostatectomy is to be recognised. It also facilitates early specific antibacterial treatment and encourages an overall awareness by the nursing and medical staff of the risk of urinary infection in prostatic patients before and after operation.

Summary

The incidence of urinary infection before and after operation for benign prostatic hypertrophy has been reviewed in 140 patients.

Repeated screening for bacteriuria was used throughout the hospital admission. Infection was present in 24% before operation and there was a significant correlation between the incidence of infection and the duration of preoperative catheterisation.

Postoperative infection developed in 31% and there was no relation between this incidence and the type of prostatectomy; specific antibacterial therapy was significantly more effective in eradicating urinary infection acquired after operation than before. At the time of discharge from the ward, 10% had infected urine, but only 3% of patients had persistent infection at follow-up 6 weeks after operation.

We wish to thank Dr J. H. Darrell, Department of Bacteriology, for his comments on this text.

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The Structure and Innervation of Smooth Muscle in the Wall of the Bladder Neck and Proximal Urethra

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Although much has been written concerning the structure and function of the bladder neck and proximal urethra, current views on the existence of an "internal vesical (or urethral) sphincter" remain widely divergent. Some of this confusion has arisen because morphologists have failed to agree upon the arrangement and innervation of smooth muscle in the region. Thus, some workers (Kalischer, 1900; McCrea, 1926; Uhlenhuth, 1953; Hutch, 1972) describe circular muscle in the bladder neck and proximal urethra which they believe forms the anatomical basis for a functional internal sphincter. Others dispute the existence of such a structure and present evidence that the muscle cells in the proximal urethra are continuous with those of the bladder and act so as to increase rather than reduce the lumenal diameter of the urethra (Wesson, 1920; Macalpine, 1934; Lapides, 1958; Woodburne, 1960; Tanagho and Smith, 1966). This concept in turn has been challenged by the results of different workers including the recently recorded observations of McNeal (1972) and Dröes (1974) who state that the musculature of the urethra is anatomically distinct from that of the detrusor of the bladder. Most of these conflicting opinions have been founded upon studies of human postmortem material which has been examined either by gross dissection or by standard histological procedures. The limitations imposed by these techniques, combined with the inevitable postmortem changes which occur prior to the fixation of such tissue, may account for some of these opposing points of view. Recently developed neurohistochemical and electron-microscopic techniques, however, circumvent some of these technical problems since structures which are known to have considerable functional significance can now be identified with certainty.

Unfortunately, the latter methods require the use of fresh tissue and this factor usually prohibits their application to studies on normal human material. Nevertheless, it is surprising to find that a combination of such procedures has not been used to examine the bladder and proximal urethra in other, more readily available, species, since such a comparative study could act as a useful guide for future research in the human. The present paper, therefore, reports our observations on a number of species and the results have enabled us to conclude that the arrangement, structural characteristics and innervation of smooth muscle surrounding the bladder neck and proximal urethra differs in a number of important respects from that of the bladder detrusor. Collectively, these findings support the concept of a discrete sphincter of smooth muscle (particularly evident in the male) which appears to be under the dual control of the autonomic nervous system.

Materials and Methods

Animals were anaesthetised using either intravenous or intraperitoneal injections of Nembutal (sodium pentobarbitone) and tissues obtained from equal numbers (totals in parenthesis) of male and female guinea-pigs (12), cats (6), and rats (10). Of these, specimens from 1 male and 1 female member of each species were processed for electron microscopy and the remainder were examined using the light microscope.

Light Microscopy

In female specimens, the urinary bladder, the distal one-third of the ureters and the proximal two-thirds of the urethra were removed *in toto* and orientated into the required plane on cryostat tissue holders. In male specimens, the same regions were removed together with the prostate, the latter in order that the relationships of the proximal urethra would be preserved. All tissues were rapidly frozen in isopentane cooled in liquid nitrogen and transferred to a cryostat maintained at −25°C internal temperature. Serial or semiserial sections 10 to 20 μm in thickness were prepared and processed either for routine histology (using Masson's trichrome technique) or tissue catecholamines or cholinesterases as outlined below.

Tissue Cholinesterases. Gomori's (1952) method was employed on sections adjacent to those treated for catecholamines. Some sections were pre-incubated at 20°C for $\frac{1}{2}$ hour at pH 7·4 in either 10^{-5}M TIPA (tetraisopropylpyrophosphoramide) or BW 62C47. All sections were placed in stock solution at pH 6·0 which contained either acetyl thiocholine iodide or butyryl thiocholine iodide as substrate together with the appropriate inhibitor at the same molar concentration. Following incubation at 37°C for 3 to 24 hours, sections were washed in distilled water, counterstained with haematoxylin, dehydrated, cleared and mounted in Depex.

Tissue Catecholamines. The method employed was similar to that described for cryostat sections by Spriggs, *et al.* (1966). Appropriate sections were placed on glass coverslips, rapidly transferred to desiccators containing phosphorous pentoxide and stored for $1\frac{1}{4}$ to 2 hours. The coverslips were then placed in closed vessels each containing 6 gm of paraformaldehyde previously equilibrated with an atmosphere of 40·5% relative humidity. Sections were then heated at 80°C for 1 to 2 hours, mounted under liquid paraffin and examined in a Vickers photomicroscope using a Wotan HBO 200 W mercury vapour lamp together with excitor filter BG 12/5 mm and barrier filters GG 4/1·5 mm and Wratten 2E.

Electron Microscopy

Small pieces of tissue were removed from the bladder fundus, bladder neck and proximal urethra of each of the animals and fixed in either:

(*a*) ice-cold 1% osmium tetroxide in acetate-veronal buffer at pH 7·3 for 1 hour (Palade, 1952); or
(*b*) 3% potassium permanganate in acetate-veronal buffer at pH 7·3 for 1 hour (Richardson, 1966).

After fixation, the specimens were dehydrated in ascending concentrations of ethyl alcohol and embedded in TAAB epoxy resin with the aid of propylene oxide. Thin sections were cut with glass knives and a Reichert OmU3 ultramicrotome, mounted on uncoated copper grids, double stained with alcoholic uranyl acetate (Watson, 1958), and lead citrate (Reynolds, 1963) and examined in a Philips EM300 electron microscope.

Results

Irrespective of the species, the results obtained in animals of the same sex are basically similar and consequently the following description applies to all the species unless otherwise stated.

Light Microscopy

In the fundus and body of the bladder, the muscle coat is composed of numerous interlacing smooth muscle bundles running in a variety of directions. Discrete layers of muscle are absent although bundles on the outer aspect of the muscle coat usually run in a longitudinal direction when compared with those situated on a deeper plane (particularly in the cat). Individual muscle bundles are relatively large and composed of smooth muscle cells closely packed together with little intervening connective tissue (Fig. 1). In the bladder neck, however, there is an abrupt transition in this arrangement of smooth muscle which occurs circumferentially and lies between the vesical orifices of the ureters and the urethra. (*N.B.* A region corresponding to the human trigone could not be identified in any of the specimens examined.) In this region, muscle cells are not arranged in large bundles but lie in small groups separated by amounts of connective tissue (Fig. 2). In both sexes the majority of these muscles run in a circular direction and extend distally to surround the proximal urethra completely. In male preparations the muscle fibres are relatively numerous and extend along the urethra as far as the ejaculatory ducts where the smooth muscle coat ends, leaving the distal portion of the urethra devoid of a similar muscle coat. In comparison with the male of the same species, the smooth muscle coat of the female is less well developed;

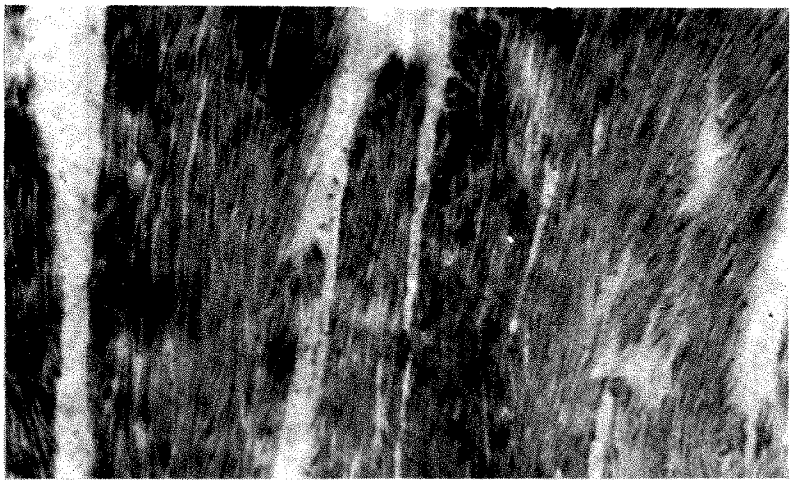

Fig. 1. This photomicrograph illustrates the large smooth muscle bundles which are found throughout the detrusor muscle of the bladder. The bundles are composed of closely packed cells with little intercellular connective tissue. This preparation was obtained from the fundus of the cat bladder. × 250.

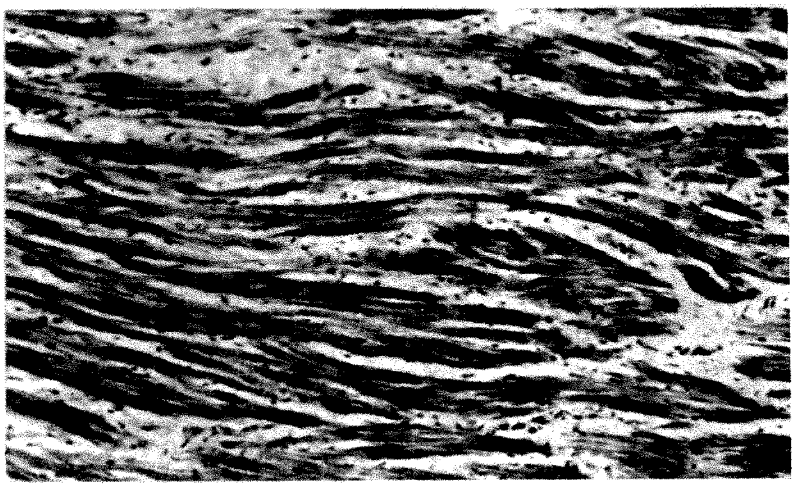

Fig. 2. In this photomicrograph of a section through the smooth muscle in the proximal urethra of the male cat the cells are arranged in small groups. Note the absence of large muscle bundles. Compare with Fig 1. × 250.

it does, however, continue throughout the length of that part of the urethra included in the present study.

Cholinesterase-positive Nerves. In all specimens, the muscle coat of the bladder is richly and evenly supplied with acetyl cholinesterase-positive (presumptive cholinergic) nerves. In the bladder neck similar nerves continue into the proximal urethra where they lie adjacent to the smooth muscle cells of the region (Fig. 3). These nerves accompany the smooth muscle coat and extend along the length of the urethra in the female. In the male, similar nerves run in the smooth muscle and can be identified as far as the entrance of the ejaculatory ducts.

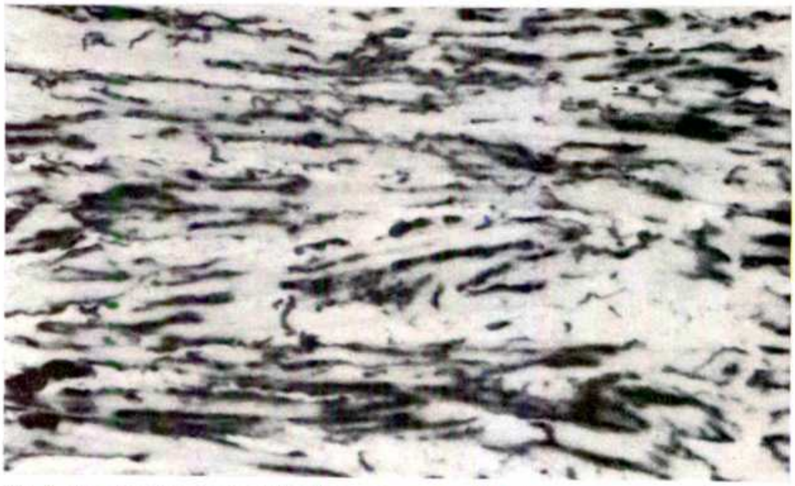

Fig. 3. An extensive plexus of AChE-positive nerve fibres is apparent among the smooth muscle cells of the proximal urethra. This preparation is an adjacent section to that illustrated in Fig. 2. × 250.

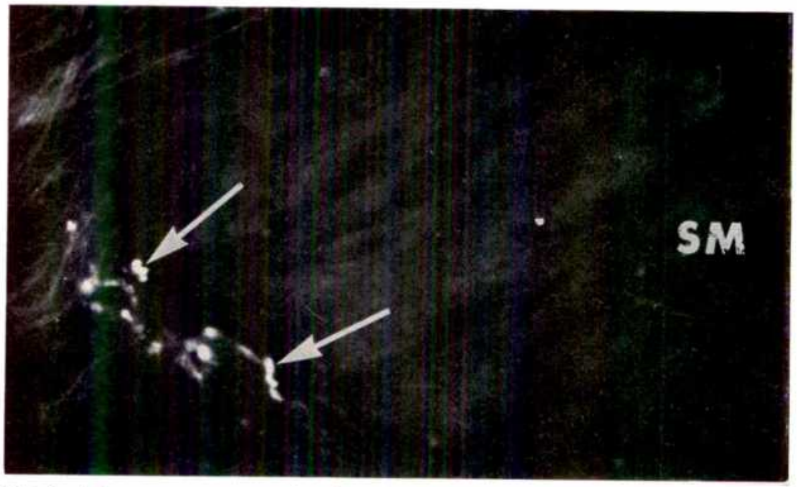

Fig. 4. A fluorescence preparation from the fundus of the guinea-pig bladder demonstrating the sparse distribution of noradrenergic nerves in this region. A few terminals (arrows) can be identified in the connective tissue surrounding the smooth muscle bundle (SM). Compare with Fig. 5. × 350.

Catecholamine-containing Nerves. Fluorescent noradrenergic nerves are rarely observed amongst the muscle bundles of the fundus and body of the bladder in the guinea-pig and rat. Those which are present usually accompany the vascular supply and run in the connective tissue which separates the muscle bundles (Fig. 4). In the bladder neck, however, (below the entrance of the ureters) a marked increase in noradrenergic nerves is evident in that region in which the change in the arrangement of smooth muscle has been shown to occur. In both sexes, this rich nerve supply continues into the smooth muscle coat of the urethra where individual terminal regions can be identified in close association with the smooth muscle cells (Fig. 5). In the male, noradrenergic nerves supplying the proximal urethra are also in continuity with those which are clearly distributed to the muscle coat of the ejaculatory ducts. In the cat, a similar arrangement of noradrenergic

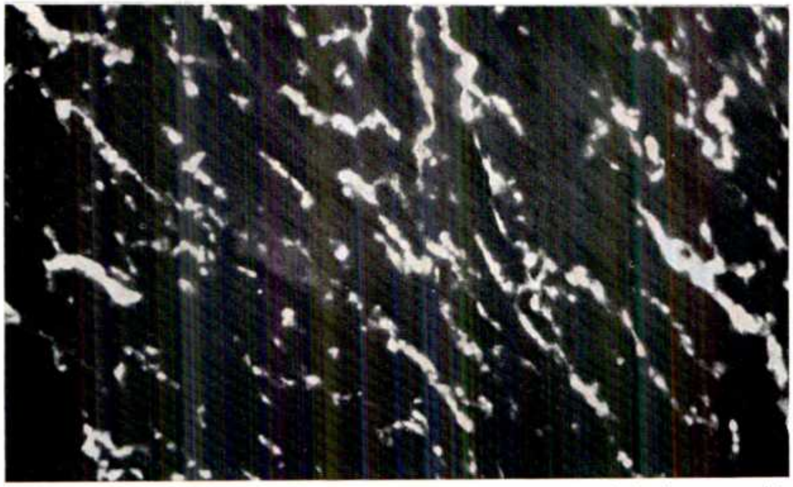

Fig. 5. Amongst the smooth muscle cells of the proximal urethra in both sexes a rich plexus of fluorescent noradrenergic nerves is clearly evident. This preparation was obtained from a male guinea-pig. × 350.

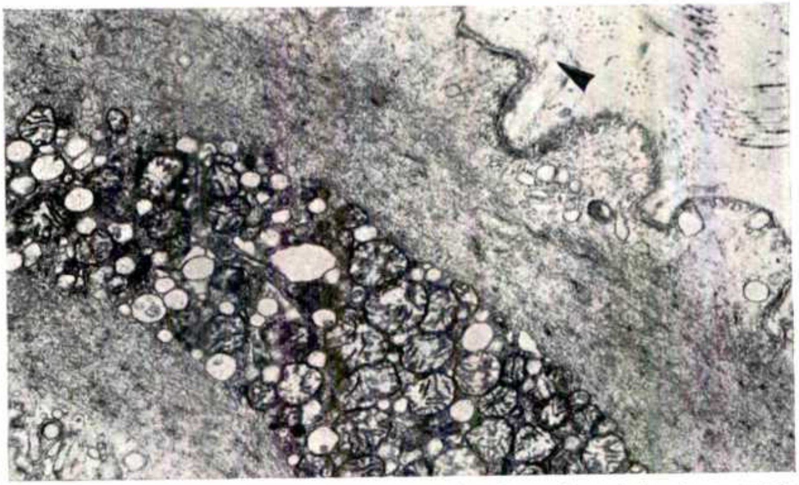

Fig. 6. A central core of densely-packed mitochondria and granular reticulum is commonly observed in the smooth muscle cells surrounding the proximal urethra. This feature is particularly prominent in the guinea-pig and is illustrated in this electron micrograph. Note the elastic fibrils at the surface of the cell (arrows). OsO_4 fixation. × 13,000

nerves has also been observed, although some of the muscle bundles which extend into the body of the bladder also possess a rich noradrenergic nerve supply in this species.

Electron Microscopy

Sections from the fundus of the bladder of all the species demonstrate the large smooth muscle bundles which are separated from their neighbours by numerous collagen fibres amongst which blood vessels and occasional fibroblasts can be observed. The smooth muscle cells forming these bundles are closely packed together and contain fine filaments and randomly arranged mitochondria. In contrast, sections from the bladder neck and proximal urethra reveal that the smooth muscle cells are arranged singly or in small groups. In cross-section, these smooth muscle cells

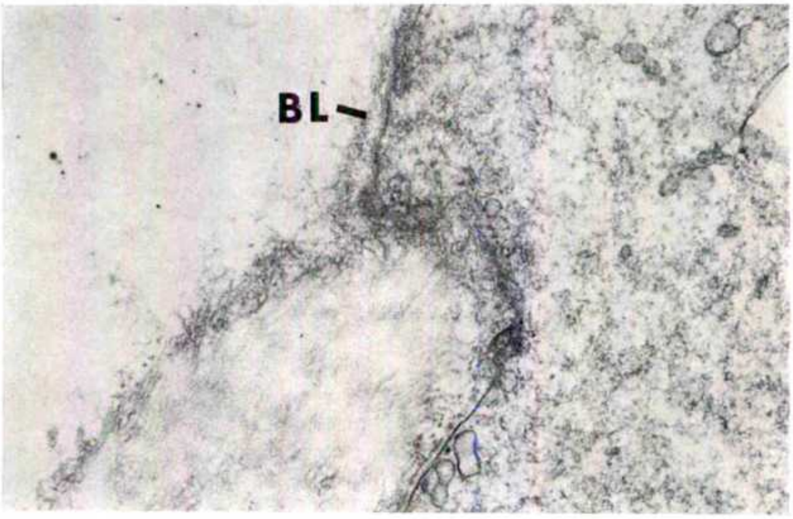

Fig. 7. In this high-power electron micrograph an elastic fibre is closely apposed to the surface of a urethral smooth muscle cell of the guinea-pig and appears in continuity with the basal lamina (BL). OsO_4 fixation × 39,000

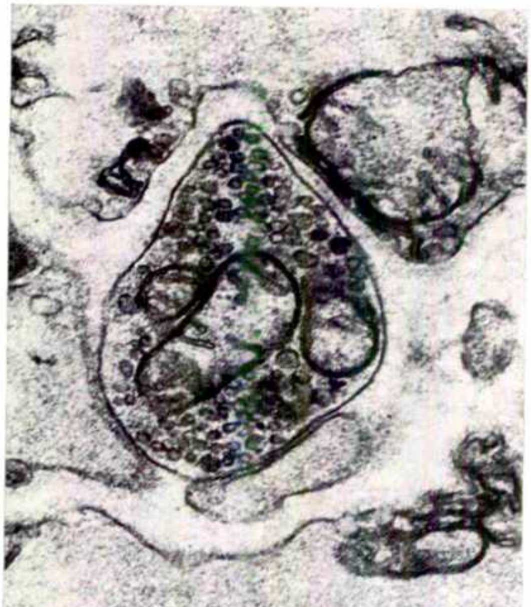

Fig. 8. Presumptive cholinergic nerve terminals packed with small agranular vesicles are frequently observed adjacent to urethral smooth muscle cells. This electron micrograph shows one of these terminals in the cat urethra. $KMnO_4$ fixation. × 44,000

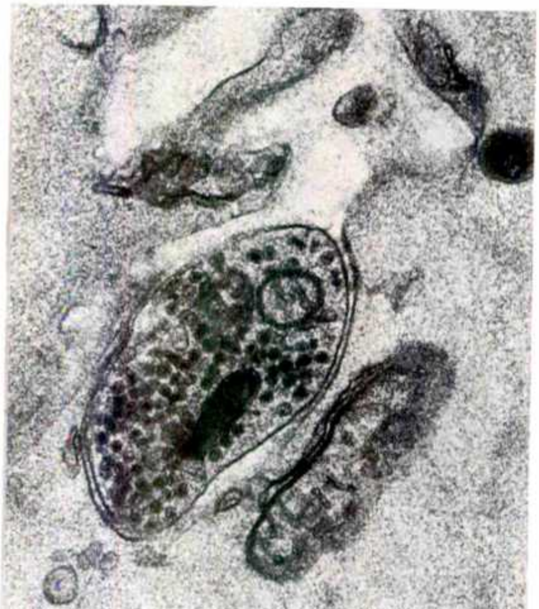

Fig. 9. Noradrenergic nerve terminals contain characteristic small dense-cored vesicles. In this electron micrograph one such terminal is observed lying in a cleft at the surface of a urethral smooth muscle cell in the cat. $KMnO_4$ fixation. × 44,00

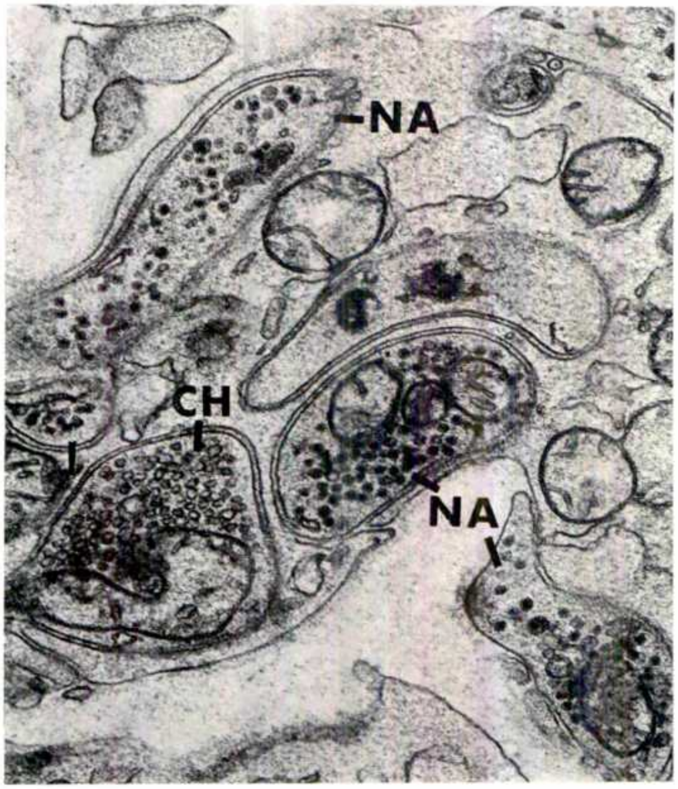

Fig. 10. In addition to single nerve terminals small nerve bundles also occur among the smooth muscle of the proximal urethra and contain both noradrenergic (NA) and presumptive cholinergic (CH) axons. This electron micrograph was obtained from the proximal urethra of the rat. $KMnO_4$ fixation. × 36,000

are irregular in outline and many possess elongated processes which form close contacts with adjacent smooth muscle cells. Peg and socket junctions are also frequently observed. A characteristic feature of these cells is an accumulation of mitochondria and rough endoplasmic reticulum at both poles of the elongated nucleus (Fig. 6).

These organelles, together with occasional Golgi membranes, often form a central core which, in longitudinal sections, may be seen to extend almost the entire length of the smooth muscle cell. A prominent basal lamina surrounds each urethral smooth muscle cell and the intercellular spaces are found to contain numerous elastic fibrils. Many of the latter appear to be in continuity with the basal laminae of the smooth muscle cells and are particularly prominent in the guinea-pig where they often lie at the surface of the cells (Fig. 7).

It is now generally accepted that 2 types of autonomic nerves can be recognised electron microscopically. This distinction is based upon the fine structure of the axonal vesicles contained within the nerve terminal. Noradrenergic axons contain numerous small (40 to 60 mm diameter) vesicles which possess a central electron dense core, while presumptive cholinergic axons possess vesicles of a similar size but which are invariably agranular. Occasional large granulated vesicles (80 to 100 nm diameter) are observed in both types of nerve. In all the specimens obtained from the fundus of the bladder, presumptive cholinergic terminals are frequently encountered between individual smooth muscle cells. These vesicle-containing axons frequently occur at the surface of the cells, separated from them by a gap varying between 20 and 100 nm. However, noradrenergic nerves have rarely been identified adjacent to smooth muscle cells in the preparations from this region. In the bladder neck and proximal urethra similar presumptive cholinergic axons have been observed amongst the muscle cells (Fig. 8). In addition, numerous noradrenergic nerves have also been identified running either singly (Fig. 9) or in groups (Fig. 10) in samples from these regions.

The 2 types of axon appear to be equally distributed and, in occasional fortuitous sections, 1 muscle cell is seen to be closely related to both types of autonomic nerve.

Discussion

The literature contains a number of accounts of circularly orientated smooth muscle which partially or completely encircles the bladder neck and proximal urethra. Some workers have considered that this arrangement provides structural evidence in favour of a sphincteric mechanism in the region. However, several other workers who have made comparable morphological observations have argued against the existence of such a sphincter. The main reason for the latter interpretation lies in the belief that the detrusor muscle is directly continuous with, and structurally identical to, that forming the bladder neck and proximal urethra (Langworthy, Kolb and Lewis 1940; Clegg, 1957; Bro-Rassmussen *et al.*, 1965; Tanagho and Smith, 1966). This anatomical arrangement clearly implies that the smooth muscle of the bladder neck and proximal urethra will contract in synchrony with that of the bladder proper (Woodburne, 1960). It is hardly surprising therefore that these workers have denied the existence of a sphincter in the region of the bladder neck, since, if such a mechanism does exist, their findings indicate that its action would oppose the contraction of the bladder during micturition. In attempts to circumvent this apparent conflict, a number of ingenious theories have been proposed. Wesson (1920) considered that the detrusor bundles formed a loop rather than a complete ring of muscle around the bladder neck and by so doing increased, rather than reduced, the diameter of the urethral lumen during bladder contraction. This concept was elaborated by Macalpine (1934) who emphasised the importance during micturition of the longitudinal muscle fibres which extended from the trigone and served to further increase the diameter of the proximal urethra. Woodburne (1960) has also emphasised the importance of longitudinal detrusor muscle which he believed to be continuous with that of the urethra and has attached little significance to the circular muscle in this region.

The results outlined in the present investigation have failed to produce support for the views expressed by the latter group of workers. Indeed, our study provides both light- and electron-microscopic evidence that distinct structural differences do exist between detrusor smooth muscle and the muscle surrounding the bladder neck and proximal urethra. It therefore seems reasonable to propose that detrusor contraction can occur without directly inducing contraction of the smooth muscle in the bladder neck and proximal urethra, and vice versa. In addition, the disposition of smooth muscle around the bladder neck and proximal urethra is clearly compatible with the view that this region, from the anatomical standpoint, could function as a sphincteric mechanism (Kalischer, 1900; McCrea, 1926; Uhlenhuth, 1953). Indeed, it seems probable that the "pre-prostatic sphincter" reported by McNeal (1972) and the "trigonal ring" as defined by Dröes (1974) in human material are analogous to the smooth muscle presently described.

In addition to these differences in the structure and arrangement of smooth muscle, the present neuromorphological findings have demonstrated regional variations in the distribution of autonomic nerve terminals in all the species examined. The functional significance of these observations in relation to the above discussion is particularly interesting and worthy of further consideration. The smooth muscle cells of the bladder detrusor are richly supplied with presumptive cholinergic ("parasympathetic") terminals, although noradrenergic ("sympathetic") nerves are usually far less frequently encountered in this situation. In contrast, the smooth muscle in the bladder neck and proximal urethra is related to both noradrenergic and presumptive cholinergic nerve terminal regions. Electron microscopy has also shown that most smooth muscle cells are closely related to autonomic nerves and provides structural evidence that effective neuromuscular synaptic transmission can occur.

In male preparations some of the noradrenergic nerves which supply the proximal urethra have also been seen to distribute branches to the ejaculatory ducts. The latter observation gives structural support to the functional concept that sympathetic nerves which cause seminal emission can also induce simultaneous contraction of the bladder neck and proximal urethra and thereby prevent reflux of ejaculate into the bladder (Elliot, 1907; Learmonth, 1931; Denny-Brown, 1936; Langworthy *et al.*, 1940; Gennser *et al.*, 1969; Stockamp and Schreiter, 1974). Tanagho, Meyers and Smith (1969) have suggested that the rise in urethral resistance which occurs during sympathetic stimulation is due to effects upon the vascular supply rather than to a direct influence upon the urethral musculature. Whilst the present study does not completely exclude this explanation, it does support the alternative view, namely that noradrenergic nerves can exert direct effects upon the smooth muscle cells in the bladder neck and proximal urethra. In this context a number of workers including Edvardsen (1968), Kleeman (1970), Raz and Caine (1972) and Nergårdh (1974) have recently demonstrated both alpha- and beta-adrenergic receptor sites on bladder neck and urethral smooth muscle cells. In the male, therefore, our observations are compatible with the general concept that the smooth muscle of the bladder neck and proximal urethra can function as an independent "internal" sphincter which is effective in preventing retrograde ejaculation.

This region is also of importance both in micturition and in maintaining continence in either sex, although its active role in these mechanisms is, at present, difficult to evaluate. Some workers (Elliot, 1907; Learmonth, 1931; Kleeman, 1970; Krane and Olsson, 1973; Stockamp and Schreiter, 1974) consider that the bladder neck and urethra are actively closed during bladder filling by the direct effects of noradrenergic sympathetic nerves upon the smooth muscle in these regions. Others (Lapides, 1958; Woodburne, 1960; Ruch, 1965) dispute this interpretation and argue that the elasticity of the tissues is sufficient to account for passive closure of the region. Unfortunately, the results of the present study are inconclusive in these respects since numerous noradrenergic nerves and abundant elastic tissue elements are both features which have helped to distinguish the bladder neck and proximal urethra from the bladder proper. Thus, from the structural viewpoint, both active and passive mechanisms could account for the closure of the bladder neck and proximal urethra.

The influence of cholinergic nerves upon the bladder outlet and urethra during these important events is equally uncertain. Recently Nergårdh and Boréus (1973) have proposed that cholinergic nerves act directly upon periurethral noradrenergic cell bodies rather than on the circular smooth muscle in the outlet region of the bladder. Our findings, however, have shown cholinergic terminal regions closely related to these muscle cells, demonstrating that a direct cholinergic innervation of this region cannot be discounted. Finally, the foregoing discussion has shown that additional research on human and animal material is essential, if the role played by the bladder neck and proximal urethra during micturition is to be finally established.

Summary

Neurohistochemical and electron microscopic techniques have been employed to compare the structure and autonomic innervation of the bladder detrusor with that of the bladder neck and urethra in male and female cats, rats and guinea-pigs. In all specimens the structure and arrangement of smooth muscle in the detrusor was different from that in the bladder neck and proximal urethra. In male specimens this circular smooth muscle extended into the proximal urethra as far as the entrance of the ejaculatory ducts. A similar muscle coat was less well developed in the female but could be identified along the length of the urethra.

Differences in the distribution of autonomic nerves have also been demonstrated. Presumptive cholinergic nerves were frequently encountered amongst the smooth muscle cells of the detrusor whilst noradrenergic nerves were relatively sparse. In contrast, muscle in the bladder neck and urethra was richly innervated by both types of autonomic nerve. In the male these findings are considered to provide support for the concept of a sphincteric mechanism which prevents retrograde ejaculation. In both sexes the possible functional role of the autonomic innervation of the bladder neck and proximal urethra during micturition has also been discussed.

We wish to thank Professor G. A. G. Mitchell, in whose department this work was undertaken, and to express our appreciation for the interest shown in this study by Mr J. Smith, Consultant Urologist, The Radcliffe Infirmary, Oxford. In addition, the skilful technical assistance of Mr R. Ellis, Miss G. Moore and Miss S. A. McIntyre is gratefully acknowledged.

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Role of Uroflowmetry in the Assessment of Lower Urinary Tract Obstruction in Adult Males[1]

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The indications for surgical relief of prostatic obstruction are usually based on the case history, clinical, endoscopic and radiological examinations. In many instances there is no clear indication for surgery. Symptoms may be minimised by the patient, who may not be aware of them because of the insidious onset of obstruction. The size of the prostate bears no relation to the degree of obstruction. Cysto-urethroscopy provides only a static assessment of an essentially dynamic process. Radiological examination may be helpful in advanced degrees of obstruction, but is of little help in early cases. It is the purpose of this paper to demonstrate the value of uroflowmetry as a useful clinical tool in the diagnosis and follow-up of prostatic obstruction.

Materials and Methods

173 patients presenting with symptoms of lower urinary tract obstruction were submitted to a prospective study over a period of 18 months following a protocol designed for computer analysis. Results were analysed on an IBM 360-40. The evaluation included: history and clinical examination, urine analysis and culture, and intravenous urography with post-voiding film. Pre- and postoperative urine flow studies were done using a flowmeter based on the principle of air displacement[2] (Picker *et al.*, 1972; Susset *et al.*, 1973). The range of normality was obtained by analysis of 300 recordings obtained from normal males using this flowmeter. A minimum of 3 preoperative flow records were obtained in each patient. Most of the curves correlated well. All traces showing an irregular pattern suggesting psychological inhibition or vesical atony were discarded from the study. Postoperative flow measurements were studied at 3 months, from 3 to 12 months and over 1 year. Again, several measurements were made which confirmed that they were comparable.

The normal range of flow rate was determined (Fig. 1), which shows maximum, minimum and mean values. These are also expressed graphically. This normal flow curve was superimposed on the patient's records to allow immediate comparison. The percentage deviation from the lower limit of normal was also calculated.

Four observations are believed to be of particular significance: maximum flow, mean flow, flow at 2 seconds and time to maximum flow (Susset *et al.*, 1973). The technique used to compare these 4 observations is presented in Figure 5. These figures were also compared with the clinical, radiological and endoscopic information.

Patients were divided into 4 groups according to the aetiology of obstruction: group I, benign prostatic hypertrophy, 122 cases; group II, prostatic cancer, 27 cases; group III, chronic prostatitis, 21 cases; group IV, urethral strictures, 3 cases.

The average age for each group was respectively 63·8, 70, 59·2 and 60 years. The average duration of obstructive symptoms was respectively for each group 38·5, 23·5, 39 and 36 months. Only cases of benign prostatic hypertrophy subjected to surgery were included in the second and

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[1] Read at the annual convention of the Canadian Urological Association, Vancouver, 9th to 14th June 1973.

[2] UF-1. Physico-Medical Systems Corp., 9250 Park Avenue, Suite M-101, Montreal, Quebec, Canada, H2N 1Z9.

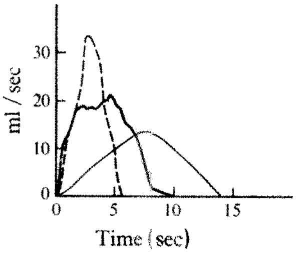

Fig. 1. Graphic recording of a normal flow curve. The maximum and minimum flow rates for this volume are shown in dotted lines. The table represents the report sent to the patient's chart for this study. The columns marked minimum and maximum are obtained from normal subjects for that volume.

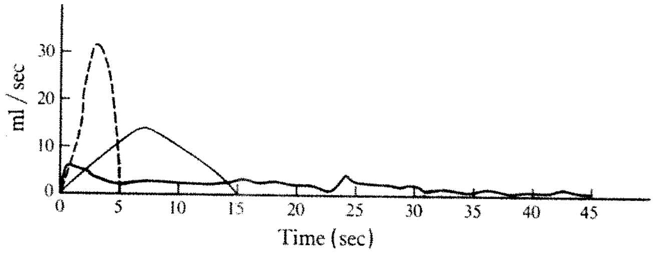

Fig. 2. Graphic recording and report of a patient with a markedly obstructive curve.

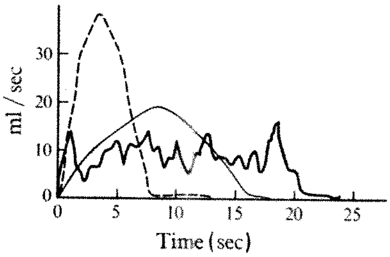

Fig. 3. Graphic recording and report in a patient with a questionable obstruction. Psychological inhibition or bladder atony could produce a similar curve.

the third period of follow-up because of the unpredictability of cancer cases and the fact that most cases of chronic prostatitis were not subjected to operation.

Transurethral prostatectomy was done in 80 patients, a retropubic prostatectomy in 18. In cases of prostatic cancer, combined treatment of transurethral prostatic resection and oestrogen or radiotherapy were carried out in 11 patients. 20 patients were treated by other methods: antibiotics, urethral dilatation, etc. Finally, no treatment was decided upon in 44 patients of these series, including 34 patients with benign prostatic hypertrophy.

Results

Figure 2 represents an example of a markedly impaired micturition. Curves of the type shown in Figure 3 were rejected from the study since it is impossible to be certain if their irregularity is due to the patient's psychological inhibition or to bladder incompetence. Atonia of the bladder is demonstrated in Figure 4, where the cystometrogram confirms the abnormally large bladder capacity. This condition is more easily revealed if the intravesical pressure is recorded at the same time as the urinary flow since it demonstrates when rises in pressure are just due to straining.

Among the 173 patients, nocturia was present in 80%, weakness of stream in 82·5% and urgency in 44·5% (Table I).

Table I

Average Preoperative Uroflowmetry

	Group I		Group II		Group III		Group IV	
Volume (cc)	192		126		310		250	
		N		N		N		N
Maximum flow (cc/sec)	9·9	14·7	7·7	11·0	16·0	18·8	16·0	17·0
Mean flow (cc/sec)	7·0	9·5	5·0	6·5	11·0	13·1	10·0	11·5
Flow at 2 seconds (cc/sec)	4·8	4·4	4·6	2·6	10·0	6·4	10·0	5·5
Time to maximum flow (sec)	9·8	9·6*	8·4	8·5*	8·9	10·8*	6·7	10·3*

N = Minimum of normal for same volume.
* = Maximum of normal for same volume.

Table II

Impairment of Flow Parameters in relation to Symptoms

	2 seconds flow	Time at maximum flow	Maximum flow	Average flow
	%	%	%	%
Frequency	40	38	82	67
Urgency	35	29	80	65
Difficulty	42	34	82	74

The average value of flow parameters before operation was compared with the lower limit of normal for a given volume.

Symptoms of prostatic obstruction were commonly associated with a reduction in the maximum flow rate, and most of these patients were finally recognised as having significant obstruction (Table V). 138 patients complained of nocturia, moderate in 44 and marked in 94. The maximum flow rate was normal in 35 of these patients. It was reduced in the remainder and reduced by more than 50% in the majority of these. This compares with the normal average flow rate in 44 patients complaining of nocturia. There is no obvious correlation between the degree of obstruction and time to maximum flow or the flow rate at 2 seconds. When compared with other clinical evidence, it was found that the maximum flow rate reflects obstruction accurately, average flow is less relevant and the other values are immaterial.

The impairment of flow parameters in relation to symptoms is presented in Table II. The 18% to 20% of patients in which the maximum flow was normal corresponds to the group of patients in whom obstruction could not further be demonstrated. It is therefore reasonable to assume that in the analysis of a urinary flow curve, the most important indicator of obstruction is the maximum flow.

The next group of results (Table III) points out the possible errors of diagnosing obstruction from the symptoms. Of 35 patients who had no nocturia, 27 (77%) presented an obstructive curve. 17 out of 30 patients who had no difficulty in micturition had objective evidence of obstruction by uroflowmetry.

It is well known that the size of the prostate by rectal examination is a poor indication of the degree of obstruction. Only 69% of 80 patients presenting moderate prostatic enlargement had reduced maximum flow and 11% of 93 patients with a grade II to III enlargement had a normal maximum flow rate.

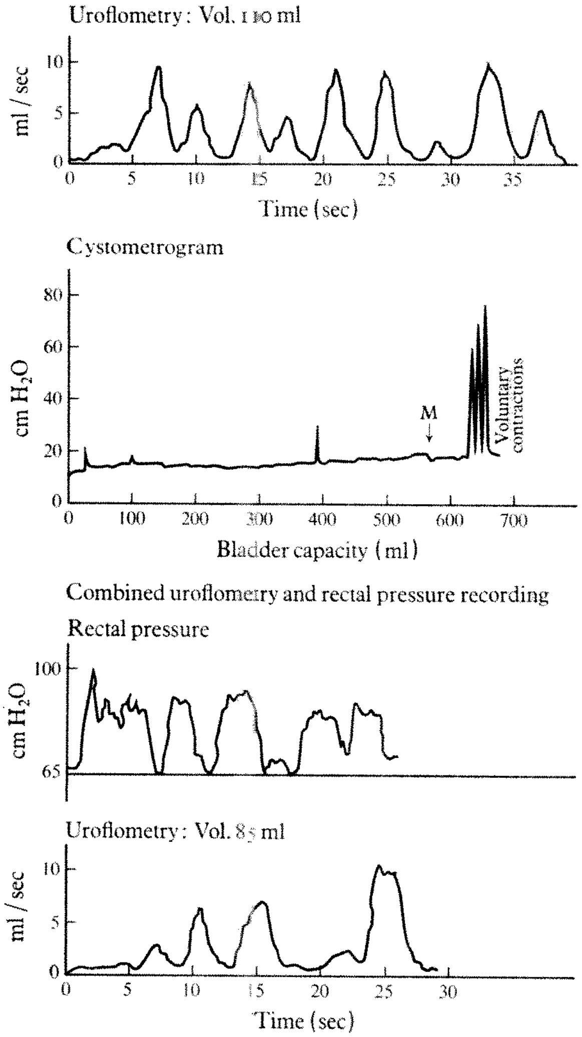

Fig. 4. Micturition study of a patient with severe prostatic symptoms showing a flow curve that is interrupted with a large bladder capacity. Simultaneous measurement of rectal pressure demonstrates the use of abdominal muscles during micturition.

The relation between the degree of bladder trabeculation as shown by cystoscopic examination and the degree of maximum flow impairment is presented in Table IV. It was found that in 50% of 60 cases where no trabeculation was noted at cystoscopy, there was a reduction of 50% or more of the maximum flow indicating significant obstruction. On the other hand, 12% of the 40 patients where the degree of trabeculation was recorded as marked presented a normal maximum flow rate. Vesical diverticula were present in 21 patients, in all of whom the maximum flow rate was reduced.

The assessment of residual urine by a post-voiding cystogram is recognised to be of value only when it is absent. If residual urine is present on the post-voiding film and the maximum urinary flow is normal, either the patient had not voided properly before the film was taken, or too long an interval was allowed before the last exposure was taken. 22% of 44 patients showing a large residual urine on the post-voiding film were shown to have normal maximum flow and absence of significant prostatic obstruction.

Table III

Obstructive Curves and lack of Obstructive Symptoms

		Obstructive curve present	
			%
No nocturia	(35)	(27)	77·0
No urgency	(96)	(75)	78·0
No difficulty	(30)	(17)	57·5

Table IV

Relation between Trabeculation and Maximum Flow

Trabeculations		Normal maximum flow rate	Maximum flow reduction ⩾50%
		%	%
Absent	(60)	25	50
Mild	(73)	21	62
Marked	(40)	12	60

The endoscopic evaluation of bladder outlet obstruction may be misleading. Among patients with no obvious prostatic intrusion 20% presented with obstructive curves.

Postoperative results were both examined qualitatively and quantitatively. Figure 6 represents a case of prostatic obstruction treated by transurethral prostatectomy. The flow curve is within normal limits at 1 month and at 5 months after operation.

The average pre- and postoperative maximum and mean flows in benign prostatic hypertrophy are shown in Table V. The maximum flow improved after prostatectomy from 32% below the lower limit of normal to 9% above this limit 3 months after the operation. It represents an average increase of 41% for the maximum flow. In the same period of time, the average flow increased by 40%.

No treatment was advised in 34 patients presenting benign prostatic hypertrophy. In 26 of them (76%) the maximum flow was normal or only within 25% of reduction in relation to the lower limit of normal. In 8 patients operation was contra-indicated by their poor general condition.

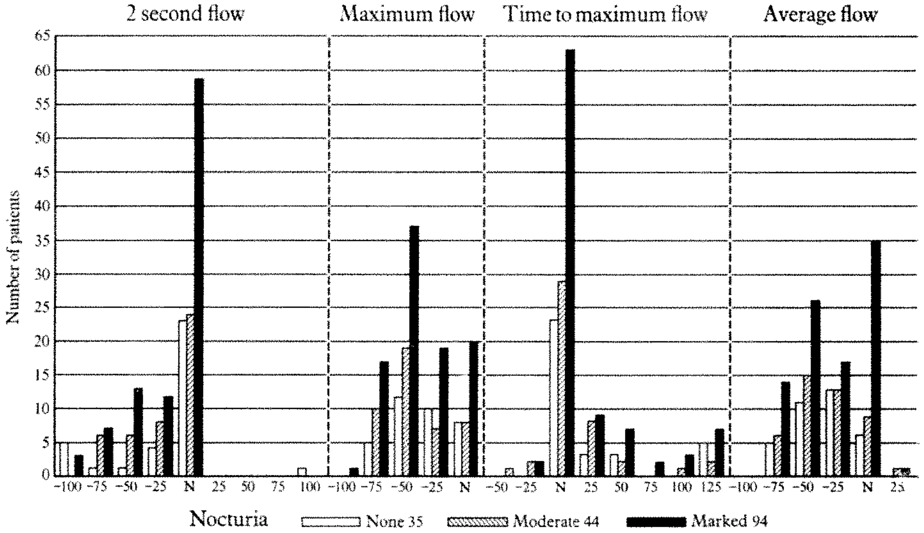

Fig. 5. An example of the statistical analysis done of the flow curve parameters in association with nocturia. The columns represent the number of patients presenting with a normal (N), more than normal (+) or less than normal (−) in each parameter.

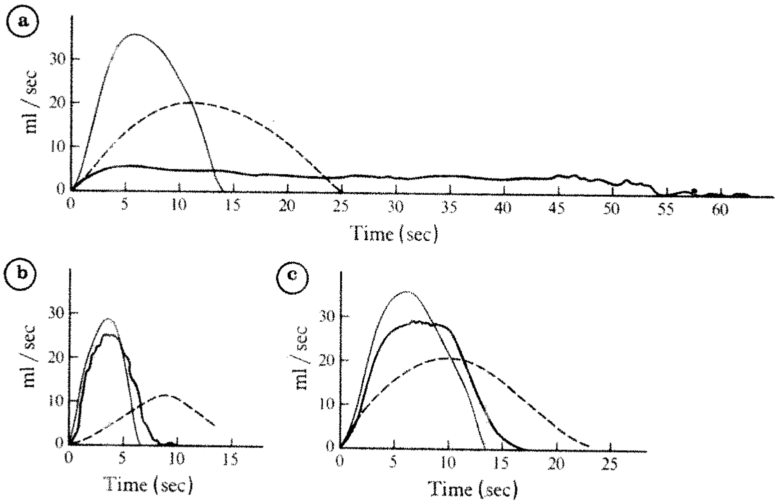

Fig. 6. Graphic recording of flowmetry pre- and postoperatively.

Discussion

Drake in 1948 described a uroflowmeter based on recording the weight of urine per time interval. He found that patients with lower urinary tract obstruction have reduced urine flow rates compared to normal subjects, and that flow rates improved markedly after operations aiming at the relief of obstruction. Von Garrelts (1958) submitted that patients with prostatic hyperplasia have flow curves which are different from normal.

Stewart in 1960, using Kauffman's uroflowmeter, was of the opinion that urinary flow measurement is of limited value in the diagnosis of lower urinary tract lesions. The inaccuracy of the latter apparatus for volumes below 200 cc may explain this attitude. Scott *et al.* (1967), using an electromagnetic uroflowmeter, studied flow rate before and after prostatectomy. They concluded that uroflowmetry is the most objective means for the diagnosis of lower urinary tract obstruction. Castro (1973) reported the parallel improvement of symptoms and flow rate following prostatectomy. The uroflowmeter based on air displacement used in this study offers the advantage of accuracy for volumes as low as 40 cc. Normal flow rates as reported by different authors vary greatly. This is to be expected since flow rate should always be related to volume.

Most urologists agree that the patient's history is not always reliable as a means of evaluating prostatic obstruction. This statistical study confirms this impression. Urethroscopy is valuable in the assessment of the size of the prostate, but its evidence is unreliable in determining treatment. Large prostatic intrusion may cause relatively few symptoms and no residual urine. On the other hand, one is frequently faced with the presence of a questionable prostatic obstruction on urethroscopy in patients presenting marked obstructive symptoms. In such instances it is often reluctantly that a transurethral prostatectomy is decided upon. The presence of an obstructive curve should allow the urologist to be more confident in reaching this decision. Chronic inflammation may simulate obstruction. The decision for surgical intervention in these cases is not straightforward, and flow measurements may be of value.

Detrusor trabeculation may be absent in prostatic obstruction (Table V), and its degree should not be the only factor used to determine treatment. On the other hand, 12% of 40 patients presenting with marked trabeculation were found to have a normal maximum flow rate. It is postulated that the detrusor reacts to prostatic obstruction in 1 of 2 ways. The majority of patients

Table V

Average Pre- and Postoperative Maximum and Mean Flow in Benign Prostatic Hypertrophy

	Preoperative (10)	3 months (50)	3-12 months (21)	>1 year (7)
Volume (cc)	192	180	172	230
Maximum flow (cc/sec)	9·9 (N = 14·7)	15·6 (N = 14·2)	13·9 (N = 13·7)	17·3 (N = 16·3)
Mean flow (cc/sec)	7·0 (N = 9·5)	10·3 (N = 9·1)	8·5 (N = 8·6)	10·6 (N = 10·9)

N = Lower limit of normal for same volume between parenthesis.

develop bladder hypertrophy and trabeculation. The majority will not. Hypertrophy is a compensatory mechanism and a normal flow rate may be maintained for many years. Frequency may become intolerable or the detrusor may decompensate resulting in urinary retention making surgery mandatory. Finally, diverticula may appear. Our 21 patients with diverticula showed obstructive flow rates which is a sign of failure of the compensatory mechanism.

Other patients, who are the minority, will not demonstrate detrusor compensatory hypertrophy. In 30 of our patients, no evidence of bladder trabeculation was shown in spite of a marked reduction in flow rate. If the obstruction is not treated it is likely that this group of patients will accumulate an increasing amount of residual urine. In the light of this hypothesis it becomes clear that some of our classical concepts of prostatic obstruction may have to be revised. Chronic retention with a smooth bladder wall apparently does not represent a later stage of prostatic obstruction with detrusor hypertrophy and trabeculation; it is infrequent for a patient with chronic retention to have a past history of marked nocturia and urgency. Furthermore, even 10 years after a prostatectomy, trabeculation is still present and has no tendency to disappear. Initial factors which determine detrusor reaction—to early hypertrophy or to early decompensation—are still unknown. The rate of the development of obstruction and the volume of fluid intake may be interesting factors to analyse.

Of the 4 parameters analysed, the best correlation with the degree of prostatic obstruction is the maximum flow rate. The average flow is less reliable although it has some value. It is interesting that maximum urinary flow appears also to be the most reliable parameter in the diagnosis of female urethral stenosis (Susset *et al.*, 1974).

It is too early to state which percentage of maximum flow rate reduction should be considered as a definite indication for prostatectomy. It was, however, found that all patients operated upon for benign hypertrophy showed a reduction of over 25% of the maximum flow rate in relation to the lower limit of normal for a given volume.

It was noted in this series that impairment of flow occurs early. 65% of patients presenting with only mild nocturia and 61% with only a slight difficulty on voiding showed over 50% reduction in maximum flow rate. We found it useful to keep a file of flow curves taken on a routine basis for patients suffering a mild degree of prostatism to follow objectively their evolution. It is hoped that this test will become of prognostic value.

Conclusions

This statistical study seems to confirm that accurate uroflowmetry is a valuable tool in the assessment of lower urinary tract obstruction in males. In our institution, we find it helpful to use uroflowmetry on a routine basis. Maximum urinary flow rate reflects bladder outlet obstruction better than other parameters. Repeated flow curves provide an easy method of follow-up of lower urinary tract obstruction and an objective assessment of therapeutic procedures. Objective evidence of obstruction has facilitated decisions on the advisability of prostatectomy.

Summary

A group of 173 prostatic patients were submitted to a prospective study to determine the respective value of symptoms, uroflowmetry, endoscopic and radiological findings in the assessment of the degree of urinary obstruction.

Uroflowmetry proved to bring objective evidence of the degree of obstruction with a reasonable degree of accuracy.

Maximum urinary flow appears to be more accurate than other flow parameters in the determination of lower urinary tract obstruction.

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Measurement of the Volume of Residual Urine using ^{131}I-Hippuran and the Gamma Camera

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The volume of residual urine in the bladder is an important factor which often needs to be determined in order to complete a diagnosis in patients with obstructive uropathy. Many methods have been described and although they provide reliable measurements of this volume most are invasive techniques. Thus, the post-micturition catheterisation of the bladder is a simple and accurate method, but may cause trauma or infection which is undesirable, particularly in patients with renal failure. Furthermore, passing a catheter into the bladder may be prevented by a urethral stricture so that in these cases direct measurement of the residual urine is not possible (Cotran and Kass, 1958; Beer, 1936).

The volume of residual urine can also be estimated by intravenous urography and the post-micturition cystogram is widely used to show the completeness of micturition. However, good renal function is required and the measurement of residual urine is unreliable by this method in patients with renal failure. The phenolsulfonphthalein test (Smith, 1960) gives an accurate measurement of the volume of residual urine provided that renal function is not impaired.

In 1961, Mulrow, Huvos and Buchanan described a new method of determining the volume of residual urine using Diodrast labelled with Iodine-131. Diodrast is rapidly excreted into the urine and the measurements of radioactivity are not difficult. The radioactive substance is injected intravenously in a dose of 10 to 20 μCi, mixed with 1 ml of unlabelled 35% Diodrast solution. Radioactivity measurements over the bladder before and after micturition are made 1 to 3 hours later, depending on the blood urea level. The difference in radioactivity before and after micturition, divided by the volume of voided urine, gives the radioactivity in each millilitre of urine. The post-micturition radioactivity over the bladder, divided by the radioactivity of each millilitre of voided urine, gives the volume of residual urine. A disadvantage of the method is that it cannot be applied to patients with hypersensitivity to Diodrast.

In 1964, Lindbjerg and Brandt applied a method based on the principle of Mulrow *et al.* (1961) using Hippuran labelled with ^{131}I. In that method a collimator was placed 25 to 30 cm from the abdominal wall before and after micturition to avoid any false measurement of radioactivity in the bladder. A difference of 1 cm in the distance from the bladder to scintillation crystal could lead to an error of up to 6%. An additional error could occur in the presence of a full bladder because of the small field of view of the collimator.

The purpose of this work was to minimise any false measurement likely to occur from the above-mentioned factors. Instead of a collimator, we have used the γ-camera and placed it in contact with the abdominal wall before and after micturition in order to obtain a more accurate measurement of the radioactivity over the bladder. Furthermore, the field of view of the γ-camera is large, so that it should be possible to measure the radioactivity over a full bladder.

Method

The following method was employed, based on the calculation described by Lindbjerg and Brandt (1964). 15 μCi of ^{131}I-Hippuran were injected intravenously and the patient was instructed to avoid micturition for 1 hour. Within the first 15 minutes after the injection, a renogram (using

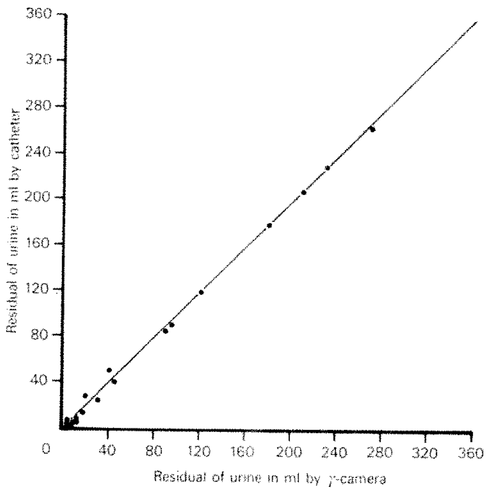

Fig. 1. Comparison of the values for residual urine obtained by Hippuran-I^{131} and catheterisation of the bladder.

standard equipment) was obtained to give an indication of renal function. 1 hour after the injection the γ-camera was lowered on to the abdominal wall and the radioactivity over the bladder was measured (Cpre): a second measurement was made over the same area after micturition (Cpost) and the volume of urine was also measured (Vu). The radioactivity over the precordium (Bkg) was recorded and the volume of residual urine was then calculated from the following equation:

$$Vr = \frac{(Cpost - Bkg)}{(Cpre - Cpost)} \times Vu$$

Patients

The method was applied to 26 unselected patients from the Urological Department. 20 were male and 6 female, the age range being 33 to 79 years. The blood urea was determined before the test. The control value was obtained by catheterisation of the bladder 5 minutes after the post-micturition measurement of radioactivity.

Results

The clinical details of the patients and the values for residual urine obtained by the γ-camera and by catheterisation are presented in Table I. The comparison between these values is shown in Figure 1; the correlation is highly significant.

Discussion

Our experience with this method has shown it to be both simple and reliable. No preparation of the patient is required and apart from the initial injection, it is non-invasive and does not disturb the patient. The only significant disadvantage is the requirement to postpone micturition for 1 hour and 1 patient in this study with severe frequency was excluded for this reason.

In contrast to other methods used to measure residual urine, this method can be applied with moderately impaired renal function. It is also a convenient method for use in those patients who are unable to micturate either due to retention of urine or to psychological factors.

Table I

Comparison of the Results of Determination of the Volume of Residual Urine with ^{131}I-Hippuran and Catheterization of the Bladder.

Case No.	Sex	Age	Blood Urea mg%	Diagnosis	Residual Urine (ml)	
					Gamma Camera	Catheter
1	M	79	75	Prostatic hypertrophy + bladder stone	88	85
2	M	65	45	Prostatic hypertrophy	4	4
3	M	42	75	Urinary infection	4·8	3
4	M	44	40	Bladder-neck obstruction	44·8	40
5	M	33	30	Renal dysplasia	0	0
6	F	40	38	Renal dysplasia	5·9	0
7	F	49	40	Urethral diverticulum	0	0
8	M	38	65	Nephrolithiasis	2	0
9	M	57	45	Prostatic hypertrophy	19·7	18
10	M	73	50	Prostatic hypertrophy	*	80
11	M	62	45	Prostatic hypertrophy	6·5	5
12	M	43	50	Bladder-neck obstruction	269	270
13	M	67	45	Bladder tumour	6·3	6
14	F	17	35	Neurogenic bladder	*	300
15	M	59	50	Bladder tumour	21	27
16	F	62	45	Bladder tumour	10·5	10
17	F	55	40	Bladder tumour	28·7	20
18	M	69	45	Prostatic hypertrophy	180	180
19	M	60	50	Prostatic hypertrophy	0	0
20	M	75	45	Bladder stone + prostatic hypertrophy	210	210
21	M	72	45	Postoperative bladder-neck obstruction	120	120
22	M	60	50	Chronic pyelonephritis	40	50
23	F	18	35	Nephrolithiasis	0	0
24	M	68	45	Prostatic hypertrophy	*	150
25	M	62	50	Prostatic hypertrophy	94	91
26	M	64	40	Bladder tumour	0	0

* These patients were unable to pass urine spontaneously.

The use of the gamma camera in the measurement of residual urine has simplified the method and increased the accuracy. The availability of the gamma camera and radio-isotope facilities will continue to limit these methods to larger centres. However, it is not suggested that this method is essential for routine clinical work but it is recommended that it is ideal for selected patients and for clinical research, where a measurement of residual urine is required.

Summary

A modification of the method of determining the volume of residual urine in the bladder using ^{131}I-Hippuran and the gamma camera is described. The method was applied to 26 patients with either normal or impaired renal function and proved to be both reliable and accurate.

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The Disinfection of Urological Endoscopes

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Whatever method of disinfection or sterilisation is preferred for urological endoscopes, the process is bound to entail some degree of trauma to the telescopes. It may be a corrosive or solvent effect of an aldehyde or alcohol, or the stress of heat on varying substances with different coefficients of expansion, or it may be the effect of pressure from an autoclaving procedure. Temperatures of 100°C or more can disintegrate lens mountings, window seals, adhesives between lens components and even damage the glass.

There are three principal methods of disinfection in use today: first, immersion in a chemical fluid; secondly, enclosure in a chamber containing a disinfecting vapour and, thirdly, some form of moist heat process, at temperatures of less than 100°C (Francis, 1959; Alder and Gillespie, 1961; Alder, Brown and Gillespie, 1966).

So often a variety of endoscopes may possibly be required for a particular operative procedure. Perhaps only one of these is actually used but the others have to be prepared in case they are required. Consequently, a process of disinfection, whereby the instrument is pre-packaged and stored in a sterile state, avoids subjecting the telescopes to unnecessary trauma of disinfection (Mitchell, 1970; Mitchell and Alder, 1970; Alder, Gingell and Mitchell, 1971).

The object of this paper is to review the current methods of disinfecting cystoscopes, referring particularly to the development in this hospital, following the routine use over the past 6 years of low temperature steam, with or without formaldehyde. First, the temperature employed was 80°C but over the past 3 years the temperature has been reduced to 73°C.

Methods of Disinfection

Immersion in Chemical Fluid

The antibacterial activity is dependent on thorough cleaning of the instrument prior to immersion in the fluid. If any coagulum, blood clot or even a film of grease or oil is left on any part of the instrument, it can act as a barrier between the organisms and the chemical, thus preventing disinfection. Furthermore, fluids cannot be relied upon to penetrate the joints of taps or locking levers. Any adherent bubbles, as can most likely occur within the tube of a cystoscope sheath, can again prevent fluid from coming into contact with the entire surface of the instrument. Even immersing the instrument vertically, as advocated by Miller *et al.* (1960) still allows horizontal taps to collect small air bubbles. However, telescopes have no internal channel which requires sterilisation, and this part of the endoscope is eminently suitable to fluid disinfection.

The chemicals in most common use today are either chlorhexidine or gluteraldehyde. Chlorhexidine (Hibitane) made up in the strength of 0·5% in 70% spirit will disinfect in 2 minutes. Freshly prepared gluteraldehyde (Cidex) will disinfect in 10 minutes at room temperature. Both solutions will require thorough rinsing of the instrument before use; this is particularly so with gluteraldehyde, to which many people prove sensitive. Chlorhexidine, being most effective in 70% spirit, will, as a result of the spirit solvent, ultimately damage the lens mountings.

The disinfection provided by chlorhexidine or gluteraldehyde will destroy all vegetative organisms, and by far the majority of urinary tract infections are due to non-sporing bacteria. Therefore, an instrument which has been thoroughly cleansed and has no joints, taps or crevices, can be adequately disinfected by means of either of these fluids.

Enclosure in Disinfecting Vapour

Although penetration by ethylene oxide is more reliable than immersion in chemical fluids, nevertheless this process is still dependent on thorough cleansing. The gas penetrates the inside of the cystoscope sheath, providing adequate disinfection of the lumen.

This method is dependent on a number of factors—namely, accurate control of the temperature, humidity, time, and concentration of the gas (Kelsey, 1961, 1963). The process can be controlled only by bacteriological methods. Evacuation of the ethylene oxide must be efficient after processing, and the instruments stored for a sufficient time to allow for evaporation of toxic residues.

Properly controlled, ethylene oxide is sporicidal and, therefore, a sterilising process. It is time consuming and, depending on the type of apparatus used, it can take from 2 to 4 hours.

Heat

Pasteurisation in a water bath to a temperature of 80°C (Francis, 1959) is an effective method of disinfecting endoscopes and heat can penetrate the taps, joints and crevices. Accurate temperature control in a small water bath was difficult, with older equipment, as the element continued to heat the bath even after the thermostat had switched off. Temperatures of 90°C were reported in pasteurisers where the thermostat cut out at 80°C. However, these disadvantages have been overcome with modern equipment.

Furthermore, with pasteurisation the instrument is not subjected to increased positive or decreased negative pressure as in an autoclave.

Certain endoscopes are claimed to be fully autoclavable. Although no harm would come to the sheath or moving parts of the endoscope, there is little doubt that the effective life of any autoclavable telescope can be extended by the use of a less traumatic process. Furthermore, the range of autoclavable telescopes is limited, and therefore the necessary discrimination between autoclavable and non-autoclavable telescopes by the Theatre Sterile Supply Unit (T.S.S.U.) staff, could readily lead to expensive damage.

Low pressure steam provides the additional advantages, first, of rapid heat penetration of the joints, taps and crevices; secondly, experiments over the past 3 years have shown that effective disinfection can be carried out at a temperature of 73°C; thirdly, the turnover time is about 20 minutes from dirty trolley to clean trolley if the autoclave is close at hand and, finally, it has the great advantage that the instrument is pre-packaged and disinfected in a foam-lined box ready for immediate use, so that each instrument is only subjected to the trauma of sterilisation after it has actually been used at an operation.

In addition to its efficient disinfecting activity, the low-pressure steam method has other practical advantages in the operating theatre, particularly the speed of disinfection, and the maintenance of disinfection during storage as a result of the type of packaging used, thus providing ready availability of the instruments.

The Prototype Transportable Low-pressure Steam Autoclave

As a result of a grant from the Department of Health and Social Security, the performance requirements for a prototype transportable autoclave (Fig. 1) were specified by us and constructed by Drayton Castle Co. Ltd. in 1966. This prototype has been in constant use since that date. Various types of urological endoscope and fibrelight cable have been disinfected many times through this apparatus. In the first instance, each type of instrument was subjected to 30 cycles and examined by experts without any damage being detected. Many endoscopes have since been disinfected only by this method since 1966, and still show no evidence of damage directly attributable to the low-pressure steam itself.

It has, however, been found that certain precautions must be observed: first, the low-pressure steam autoclave should have a device for monitoring audibly, visually and with an automatic

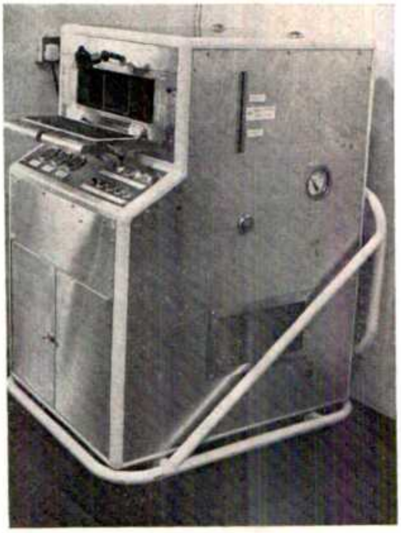

Fig. 1. Small transportable low-pressure steam disinfector ready for use.

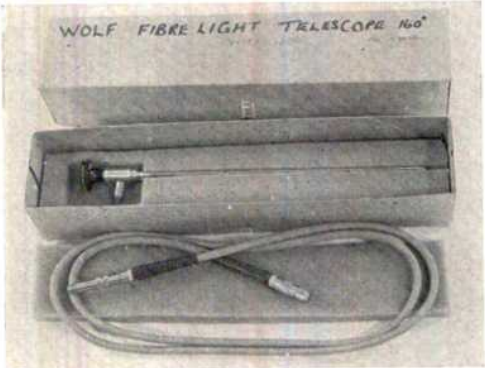

Fig. 3. Packaging of endoscopes for disinfection and storage.

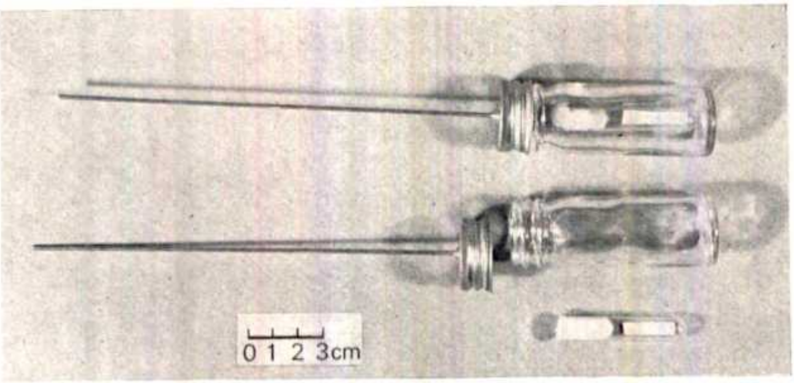

Fig. 2. Simulator test pieces (against centimetre rule).

cut-out to ensure that the temperature is never allowed to exceed 2° above the optimum disinfecting temperature of 73°C. (Note that this is only 36°C above body temperature as compared with boiling, which is 63°C above body temperature.) Secondly, the cardboard boxes used for enclosing the instrument must be prepared by extracting all the bitumen content. This can be done very simply by autoclaving the boxes at 130° to 134°C in a porous-load hospital autoclave. If a new box is used inadvertently, then bitumen will be deposited on the surface of the endoscope, making the instrument tacky to touch. Thirdly, no telescope which has previously been disinfected in chlorhexidine and spirit or gluteraldehyde should be passed through the low-pressure steam autoclave, as these telescopes may have weakened sealing on the windows which, with the reduced pressure of the autoclave, could dislodge the windows and allow steam to enter the endoscope.

Disinfection of the instruments at 73°C can be amplified to sterilisation by the addition of a formalin cycle. This will increase the cycle time to an hour and a half. The process is sporicidal to all exposed surfaces, and even in the depths of a long, fine tube but may not be lethal to spores on tight-fitting interfacial surfaces, such as taps and joints.

However, 73°C of steam alone will destroy all vegetative organisms. Heat will also penetrate all taps, joints and crevices, destroying all vegetative organisms on tight-fitting interfacial surfaces.

The procedures for operating the autoclave with steam only or with the combination of formaldehyde and steam are as previously described (Alder, Gingell and Mitchell, 1971), except that the working temperature has been reduced from 80° to 73°C. It should be stated that commercially available low-temperature steam and formaldehyde sterilisers usually operate at 80°C for 2 hours 20 minutes. It is a simple engineering process to adjust the operating temperatures, pressure and exposure times so that the machines can work at any temperature from 70°C upwards for any length of exposure time. We have been operating our machines at 73°C with an exposure time of 2 hours for about 3 years; previously they were at 80°C. Automatic devices have also been fitted by our Group Hospital Engineer which stop the procedure should the temperature in the autoclave rise 2°C above the operating temperature and at the same time giving visual and audible warning signals that a fault has occurred.

The variety of instruments thoroughly tested include: urological endoscopes manufactured by one American firm, two German firms, and three British firms, Endoscopes with conventional illumination as well as fibrelight cables and telescopes have been tested.

Testing the low-pressure Autoclave

Simulators have been designed by us to test the efficiency of these autoclaves. They consist of: first, a screw-capped chamber of about 28 ml capacity with a 7-inch (17·8 cm) length of 1 mm bore tubing soldered into the metal lid. Figure 2 illustrates the test piece, which was constructed from a standard glass Universal container, commonly used in bacteriological laboratories. Cultures of bacteria on sterile filter-paper strips were placed in small (53 × 9 mm) cotton-wool plugged, glass tubes and inserted in the glass chamber of the test piece. The test piece and culture was sealed inside a paper bag and placed in the foam-padded cardboard box, similar to the ones in routine use for cystoscopes (Fig. 3). The steam, or formaldehyde and steam, had to pass through the packaging materials, along the tubing to the glass chamber, to kill the cultures inside. Secondly, to simulate the conditions of interfacial surface such as contaminated taps and joints, the threads of small nuts and bolts (approx. $\frac{1}{2}$ × 1/8 inch) were smeared with serum suspensions of the organisms and dried. The nuts and bolts were assembled, sealed in paper bags and foam-lined boxes and exposed in the autoclave with the cystoscopes.

Test Organisms

In the chambers of the simulators the test organisms consisted of *B. stearothermophilus* spore strips (Oxoid Ltd., Southwark Bridge Road, London, SE.1) and spore culture preparations of *B. subtilis var. globigi* (Steriseal Ltd., Redditch, Worcs.) for exposure to formaldehyde and steam. For tests carried out with steam only, 25 × 6 mm sterile paper strips were well smeared with overnight cultures of *streptococcus faecalis* grown on McConkey agar.

The threads of the nuts and bolts were smeared with cultures of *B. stearothermophilus* spores (kindly supplied by Oxoid Ltd.) or of *streptococcus faecalis*, harvested from overnight growths on McConkey agar, which had been suspended in sterile 50% normal horse serum in normal saline.

The Result of Tests for Surviving Organisms

Following exposure to formaldehyde and steam at 73°C for 2 hours, *B. stearothermophilus* and *B. subtilis var globigii* spores were always killed inside the chambers of the simulators, but some spores survived inside assembled nuts and bolts. All cultures of *streptococcus faecalis* were killed on both types of simulators. With steam only, *streptococcus faecalis* was killed in both types of simulators in 15 minutes.

Another type of test piece in the form of a helix of a long length of metal tubing was suggested by Line and Pickerill (1973). Similar results were achieved with a wider variety of spore cultures exposed to steam and formaldehyde at 70° to 73°C thus confirming our previous results.

Tests for Formaldehyde Residues

Tests for formaldehyde residues were carried out by processing 6-inch lengths of PVC tubing, sealed in paper bags. Afterwards, they were tested for aldehyde residues by the method described by Gibson, Johnston and Turkington (1968). Aldehyde residues did not exceed 0·45 parts per million (0·45 micrograms per gram of tubing). This was a similar figure to that obtained after PVC tubing had been washed with detergent and rinsed for 3 hours in warm water (Personal communication—Public Analyst, Public Health Laboratory, Bristol).

Conclusion

The effectiveness of this process has been thoroughly tested and has been in regular use at the Bristol Royal Infirmary over the past 8 years. Damage to endoscopes has, in point of fact, been reduced because the instruments are stored in a protective foam-padded box (Fig. 3). Damage to endoscopes is proportional to the number of people who handle the instrument. With the use of a small transportable low-pressure steam autoclave, such as the prototype in Figure 1, which can be used either within the operating theatre itself, or just outside, the instruments need only be handled by the surgeon himself and the nurse who unpacks the box, cleanses the instrument, checks and puts it straight back in its packing. Provided the nurse who handles this instrument at the time of the endoscopy is trained as an endoscopy nurse, the useful lives of these telescopes should be considerably prolonged, and the cost of repairs to the National Health Service vastly reduced.

The temperature level should not exceed 73°C, which achieves disinfection of all vegetative organisms. The addition of the formalin cycle can provide full sterilisation. By exceeding 73°C the instrument is subjected to unnecessary heat trauma and there is no improvement in the disinfecting efficiency.

The advantages of a small autoclave over the larger autoclaves with special cycles for low-pressure steam, is in speed of operation, transportability, economy in running cost, and the fact that it can be brought close to the site where it is required for use, so reducing the handling of the endoscopes. When the packaged instrument is removed from the low-pressure steam autoclave, it will be dry, disinfected, and available for immediate use, provided the apparatus is properly maintained and operating efficiently. Any new design of low-pressure steam autoclave should be thoroughly tested by the use of simulators and thermocouple temperature measurements. When steam and formaldehyde are used, checks should be made on the efficient evacuation of steam and aldehyde.

Addendum: In recent weeks economies in fuel used in our Central Boiler House have resulted in lower mains steam pressures and wetter steam, for all types of steam sterilisers, producing condensation problems. Because of this, we have temporarily reverted to using low-temperature steam at 80°C to reduce condensation and to provide extra heat for an extended drying period.

We wish to acknowledge the help and advice received from Professor W. A. Gillespie, Dr J. C. Kelsey, Messrs A. Bishop, K. M. Henfrey and M. I. Lees. We also wish to thank our colleagues in the Department of Urology in Bristol—Mr Norman Slade, Mr Michael Roberts, Mr Roger Feneley and Mr Clive Gingell—for their helpful co-operation in this work.

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Short Case Report

Leiomyosarcoma of the Prostate

A 63-year-old man presented with frequency and hesitancy of micturition for 3 months. He never had any acute retention of urine. Physical examination revealed a non-tender distended urinary bladder and a smooth softish non-tender mass continuous with the left lobe of the prostate. The median groove of the prostate was palpable, and its right lobe was within normal limits. Serum alkaline and acid phosphatase and blood urea were within normal limits. An intravenous pyelogram showed normal excretion with calyceal system and ureters looking normal. The urinary bladder was displaced to the right by external pressure (see Fig. 1).

Suprapubic exploration on 3rd April 1973 revealed a mass arising from the pelvis with apparent continuity with the left side of the bladder wall. The bladder was opened and mucosa found intact. Careful dissection showed the tumour to be extra-vesical, and arising from the left lobe of the prostate. The removed tumour was found to be encapsulated except at its attachment to the prostate, and measured 12 cm × 11 cm × 7 cm. Histology showed highly cellular tissue and fibroblasts and muscle fibre consistent with the diagnosis of leiomyosarcoma (See Fig. 2). At his last follow-up on 28th July 1974 he was well, with no sign of recurrence.

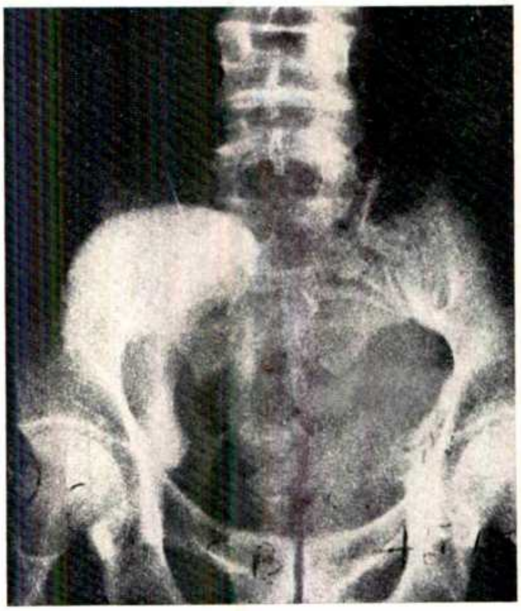

Fig. 1

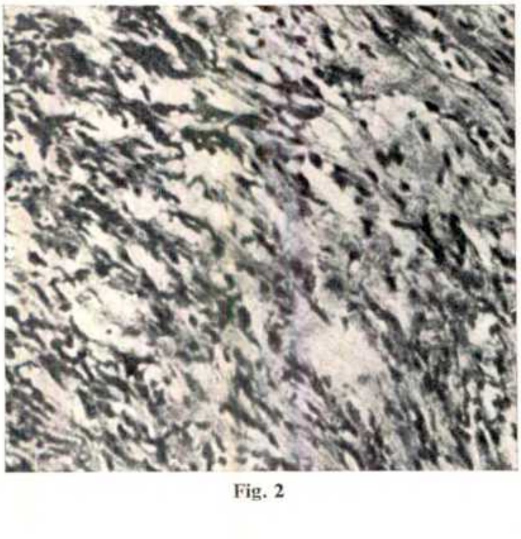

Fig. 2

Comment

Leiomyosarcoma of the prostate is rare, constituting 0·1% of prostatic malignancies (Stirling and Ash, 1939). Few patients survive for more than 7 months after diagnosis (Longley, 1955).

Anil Chandra Chatterjee
Goa Medical College, Panaji, Goa, India

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Short Case Report

A Unique Presentation of Malignant Tumours of the Urogenital Tract

Although hypernephroma can occur at any age, more than 90% occur past the age of 40 years. Although no age group is exempt, the peak instance of malignant tumours of the testis is between 20 and 40 years.

Case Report

A 60-year-old white male presented on 20th June 1974 with a painless swelling of the right testis noticed accidentally about 10 days previously. The right testis was markedly enlarged, smooth, rubbery in consistence and heavy with markedly diminished sensation. A chest X-ray was negative. Assay of urine for chorionic gonadotrophin-like activity was normal.

An IVP showed a space-occupying lesion in the upper pole of the left kidney. Urinary cytology was negative.

A right orchidectomy through an inguinal incision was performed on 24th June 1974. A left retrograde pyelogram at the same time showed distortion of the upper pole calyces. A renal angiogram showed a tumour circulation in the mass which had extended beyond the renal capsule medially. An inferior venacavagram showed no evidence of involvement of the left renal vein or inferior vena cava by tumour mass. A lymphangiogram showed metastatic deposits in both para-aortic regions presumably from the testicular tumour. A bone scan showed no metastatic lesions.

2nd July 1974. Radical nephrectomy. The tumour was found to be related to the medial aspect of the upper pole of the left kidney. There was no evidence of clinical spread outside the capsule.

Pathology Report

Right Testis. On gross examination the tumour had completely replaced the normal testicular architecture.

Microscopically the pattern was that of a classical seminoma of the testis. It did not appear to have extended up the spermatic cord.

Left Kidney. The upper pole was occupied by a typical clear cell carcinoma and this was confirmed microscopically.

A postoperative course of radiotherapy 3560 rads to the right pelvic region and 3105 rads to the para-aortic region in 19 and 21 treatments respectively was given

At follow-up 4 months later he was well with no clinical evidence of recurrence. However, a chest X-ray showed a hazy mass behind and slightly to the left of the manubrium and a week later a left supraclavicular lymph node enlargement was noted. Biopsy showed metastatic deposits consistent with seminoma.

A further course of radiotherapy with a total dose of 3500 rads was given to the mediastinum and left supraclavicular region.

Comment

Extensive review of the literature failed to show any report of the simultaneous presence of both hypernephroma and seminoma in the same patient.

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British Journal of Urology (1975), **47**, 579 ©

Short Case Report

Meso-appendicular Testis

A 41-year-old man, married and father of eight children, was admitted because of abdominal pain located in the right lower quadrant of 18 hours' duration, accompanied by temperature. He was known to suffer from chronic pyelonephritis, renal failure and hypertension and was a candidate for haemodialysis treatment. The right lower abdomen was tender on pressure with defence and a definite positive rebound sign. Rectal examination showed tenderness on pressure on the right side. The left testis was normal in size and consistency. The right scrotal sac was undeveloped.

A diagnosis of acute appendicitis was made. At laparotomy through a MacBurney incision, the vermiform appendix was markedly inflamed; in addition, in the meso-appendix, an oval tumour measuring 4 cm × 4 cm, smooth and with a rubbery consistency was found. The appendix together with the above-mentioned tumour were excised. The post-operative course was uneventful.

The appendix showed acute ulcero-phlegmonous inflammation. The small ovoid structure appeared to be testicular tissue. The tubules showed thickening of the basal membrane, and contained Sertoli cells only, without any spermatogenic cells. Groups of preserved Leydig cells were present in the interstitial tissue. In addition, a small normal epididymis was found attached to the testis.

Comment

This appears to be the first case described in the literature in which abdominal testis was found in the meso-appendix. This unusual case emphasises the fact that in cases with undescended testis in which the surgeon is unable to find the testicle, the diagnosis of agenesis of the testis should not be established immediately. Laparotomy should be performed in order to ascertain that the testis is not higher up in the abdominal cavity.

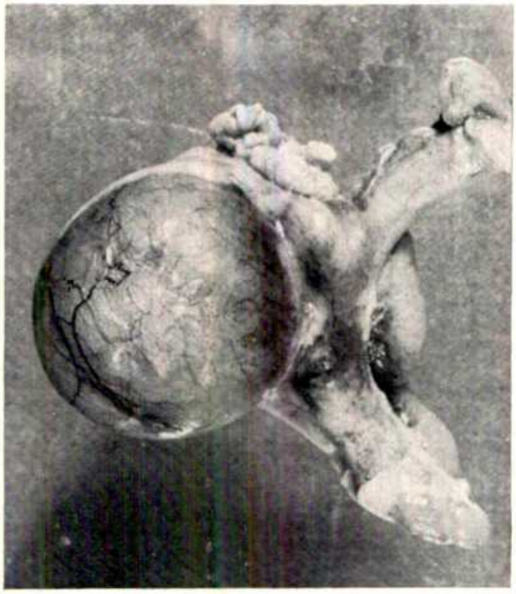

Fig.

A. Zelikovski, J. Abu-Dalu, and I. Urca
Surgical Department "B", The Beilinson Medical Center, Petah Tiqva and Tel Aviv University Medical School, Israel.

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British Journal of Urology (1975), **47**, 580 ©

Short Case Report

Pilonidal Sinus of the Prepuce

Case Report

Mr G. N., 59 years, was found to have a mass, clinically a carcinoma of the penis, lying in the corona beneath a congenitally irretractable foreskin. He had an 8-month history of enlargement of the end of the penis and of a purulent discharge.

A dorsal slit and biopsy of a hyperkeratotic area was performed (Fig. 1). Considerable free hair and clothing debris were noted as well as 2 sinuses on the ventral aspect of the prepuce. The biopsy showed hyperkeratotic changes only and was repeated twice before a sinus containing hair was transected revealing the diagnosis (Fig. 2). The lesion was treated by circumcision and dissection of the fibrous mass from the penis.

Comment

Yates-Bell (1968) has recorded a pilonidal sinus of the penis but a sinus developing beneath the prepuce has not been previously recorded. Its occurrence in a hairless area is in keeping with the acquired theory of pilonidal sinus expounded by Patey and Scarff (1946). Its resemblance to carcinoma is noted and the importance of confirming the diagnosis of malignancy by biopsy is underlined.

I would like to thank Mr J. Burke for his permission to publish this case.

J. D. RITCHIE, *St. James' Hospital London.*

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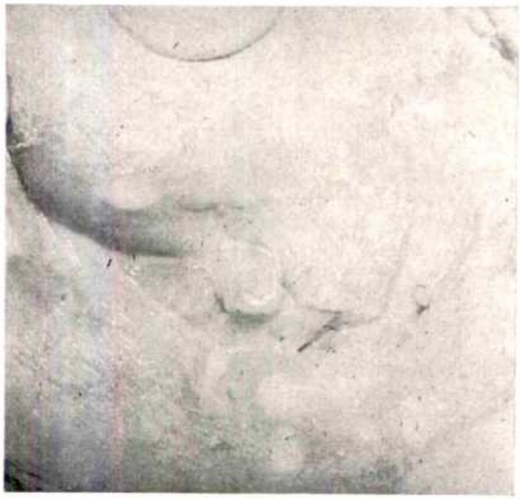

Fig. 1

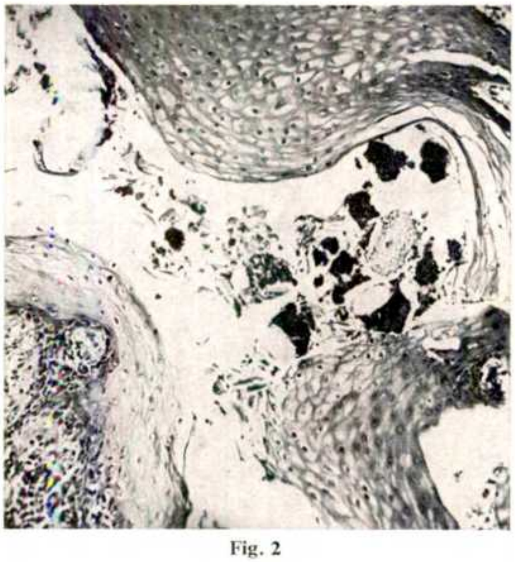

Fig. 2

Book Reviews

A Course in Renal Diseases. By G. M. BERLYNE. 4th Edition. Pp. 413. Oxford: Blackwell. 1974. £3·75

This short textbook of nephrology is directed at physicians working for MRCP and keener undergraduates but is equally suitable for urologists brushing up on their sister subject. The author describes it as "semi-programmed". Programmed learning is intellectual snakes and ladders but guided by science, not chance. After each short section the reader is asked a question which tests his understanding and retention of the facts; a right answer takes him up the ladder to the next section, a wrong one down the snake for some corrective reading before he gets back to the same place. At first I was sceptical about this approach to renal disease. Much of the clinical practice was empirical and could not be built up logically from known anatomy, physiology etc. This has become less true in the 9 years since the first edition of Berlyne, particularly in a few fields like glomerulonephritis where clinical medicine is acquiring a scientific basis. Programming a text is like setting multiple choice questions; there is a tendency to choose questions which have a definite answer, regardless of their clinical relevance, and wrong alternatives sometimes sound contrived. One can find examples of both defects in this book but you have to look harder with each edition.

After repeated exposure to the book, as reviewer and through the eyes of my postgraduate students, I have become completely converted. I am now convinced that even this degree of "semi-programming" (*i.e.* testing only a sample of the facts and ideas) makes a short factual book more stimulating and enforces self-discipline in reading. Whatever the question at the end of the section, it concentrates the mind wonderfully to know you have to face one.

A combination of high sales and Professor Berlyne's untiring energy have made the book an outstanding success. He has maintained his principle of "no reprints, only new editions" and has adhered to a demanding schedule of a thorough revision every 3 years. He looks like remaining top of the nephrological pops. The price is incredibly low—even in these hard times it should be within the grasp of any urologist looking for some holiday reading!

D. N. S. K.

Detection, Prevention and Management of Urinary Tract Infections. By CALVIN M. KUNIN. 2nd Edition. Pp. xiii × 370 with 65 illustrations. London: Kimpton. 1974. £2·85.

This book provides a comprehensive description of the problems associated with urinary tract infections and will be of use to clinicians, microbiologists, nurses and undergraduates alike. The description of the various disease processes associated with urinary tract infections is followed by sections on the bacteriological diagnosis, further investigations and management of such patients. Chemotherapy is also dealt with fully and concisely. There is a very useful chapter on screening for asymptomatic bacteriuria, which concludes by setting out the requirements for a successful screening programme for schoolgirls, which is very carefully defined.

There is little in the book which one would criticise, but the statement that tetracyclines are not contra-indicated in pregnancy would be treated with reservation by many in this country.

(*Reviewer's Note*: The binding of the copy sent for review was rather poor and one felt that with relatively little usage the pages could begin to work loose).

H. R. I.

Surgery of the Anus, Rectum and Colon. By J. C. GOLIGHER. 3rd Edition. Pp. 1172. 608 illustrations. London: Baillière Tindall. 1975. £21.

At first sight this appears to be an outstandingly excellent book, and when one looks at the many paragraphs on the genito-urinary aspects, this initial impression is amply confirmed. It is rarely that one finds so little to criticise about the statements relevant to one's own specialty in a textbook on someone else's discipline.

The management of operative injuries to the ureter, the bladder and the urethra are well presented. Even the indications for ligaturing the injured ureter sound acceptable, though most urologists would now think that implantation into the opposite ureter should have pride of place in the management of high injuries.

The effects of excision of the rectum on potency and fertility and the possible mechanisms of their production are thoroughly described and discussed. The problems of the denervated bladder are for once not underestimated.

Professor Goligher has a vast personal experience and is renowned for his clear and balanced presentations. This textbook is a model for other specialties. It is obviously excellent value, though at the price the urologist is more likely to consult it in the library than to have it on his shelf at home.

W. K. Y.

Recent Advances in Renal Physiology and Pharmacology. Edited by L. G. Wesson and G. M. Fanelli. Pp. 388 with figs., tables. Lancaster: M. T. P. 1974. £11.00.

This book consists of a series of articles based on papers presented at the Fifteenth Annual A. N. Richards Symposium held in May 1973 in Philadelphia. This origin gives it the advantage of being fairly up to date and of having chapter authors who are acknowledged experts in their field. It carries the slight disadvantage that there is inevitably some overlap, for example the effect of angiotensin antagonists is covered both by Dr Sweet and Dr Needleman, fortunately without contradictions. Although much of the material presented will be published elsewhere, the book has the advantage of allowing fuller presentation and discussion of data and is worthwhile. Minor criticisms are always possible, in particular Dr Sweet in discussing 1-Sar 8-ile angiotensin II did not mention its effect on aldosterone secretion, a piece of information of potential importance in discussing the failure of the angiotensin antagonist to correct long-standing renal hypertension in animals.

The evidence on which Dr Needleman attributed a vasoconstrictor function to angiotensin I itself was not convincing in particular since he made no mention of angiotensin II in renal lymph. Overall the book provides a valuable review of renal physiology for physicians and physiologists working in the field.

R. W.

Discussion of Previous Papers

Incomplete Urethral Duplication and Urinary Retention

By G. J. FELLOWS and J. H. JOHNSTON. (1974, **46**, 449-452).

Arnold H. Colodny and Robert L. Lebowitz: We have been very interested in duplication of the urethra and conditions that mimic this entity and have recently submitted the report of our experience (Effman, Lebowitz and Colodny). It was with interest, therefore, that we read the present paper. In our opinion, Figure 4, Case 1, resembles a dilated Cowper's duct (Currarin and Fuqua, 1972) and not partial duplication at all. We wonder if this boy might not have had a retention cyst of Cowper's duct which was disrupted at the time of endoscopy. Then, when urethrography was performed, contrast material was able to reflux back into the now open dilated duct. Such filling of Cowper's duct has been observed not infrequently during otherwise normal voiding studies. Similar cases have been described and successfully treated transurethrally in your country (Fenwick, 1896) and by us on several occasions (Colodny, Lebowitz and Welch)

We believe that many anterior urethral channels have been mistakenly called examples of partial urethral duplication or anterior urethral diverticula when they really represented dilated Cowper's ducts.

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Colodny, A. H., Lebowitz, R. L. and Welch, K. Retention cysts of Cowper's duct. To be presented at the Annual Meeting of the New England Section of the American Urological Association.

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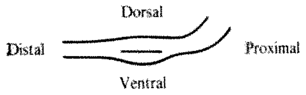
Fenwick, E. H. (1896). Retention cysts of Cowper's glands as a cause of chronic gleet, spasmodic stricture, organic stricture, extravasation of urine and of so-called "false passages" in the bulbous urethra. *British Medical Journal*, **1**, 4-6.

J. H. Johnston: I am grateful to Dr Colodny and Dr Lebowitz for their comments on the first case described by Mr Fellows and myself in our article on Urethral Duplication. Our preoperative diagnosis in this boy was in fact that of diverticulum of the bulbar urethra. However, at operation the exterior of the urethra appeared perfectly normal. When the urethra was opened it was seen that there was a double channel over a length of some 1·5 cm. The ventral channel was narrower than the dorsal and it communicated widely at *both its extremities* with the normal urethra proximal and distal to the abnormality (see diagrams of sagittal section through the urethra).



There was no extension of the ventral channel towards Cowper's gland. In effect, therefore, the lesion was indeed a limited duplication of the urethra. That it started off as a Cowper's duct which became dilated for some reason and then acquired a second opening into the urethra whilst losing any communication with Cowper's gland is possible but does not seem to me to be very likely. Instrumentation of the urethra was carried out by me before surgery but without the slightest difficulty and I am quite sure I did not force the instrument into a diverticulum and then back into the normal urethra. I still prefer our diagnosis of localised urethral duplication of developmental origin.

Department of Paediatric Urology
Liverpool Regional Urological Centre

Conferences and Courses

1st INTERNATIONAL CONGRESS OF ANDROLOGY

The Congress, organised by the Comité Internacional de Andrologia (CIDA), will be held in Barcelona from 12th-15th July 1976.

The official languages will be English and Spanish with simultaneous interpretation.

Enquiries should be addressed to: Apartado 24005, Barcelona, Spain.

ROYAL SOCIETY OF MEDICINE: SECTION OF UROLOGY

Programme 1975/76

23rd October	Presidential address by W. Barr Stirling, FRCS
27th November	Short papers
22nd January	Pathology lecture and clinico-pathological meeting
26th February	Short Papers
25th March	Hypertension (Meeting at St Mary's Hospital, W2)
22nd April	The pelvic ureter (Joint meeting with Selection of Obstetrics and Gynaecology)
27th May	Annual General Meeting and Winsbury White Lecture by Professor W. Lutzyer

Further details from:

Hon. Secretary, Section of Urology,
Royal Society of Medicine,
1 Wimpole Street, London W1.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal, i.e.*, in anatomical order beginning with papers on the kidney.

A general section is included at the end

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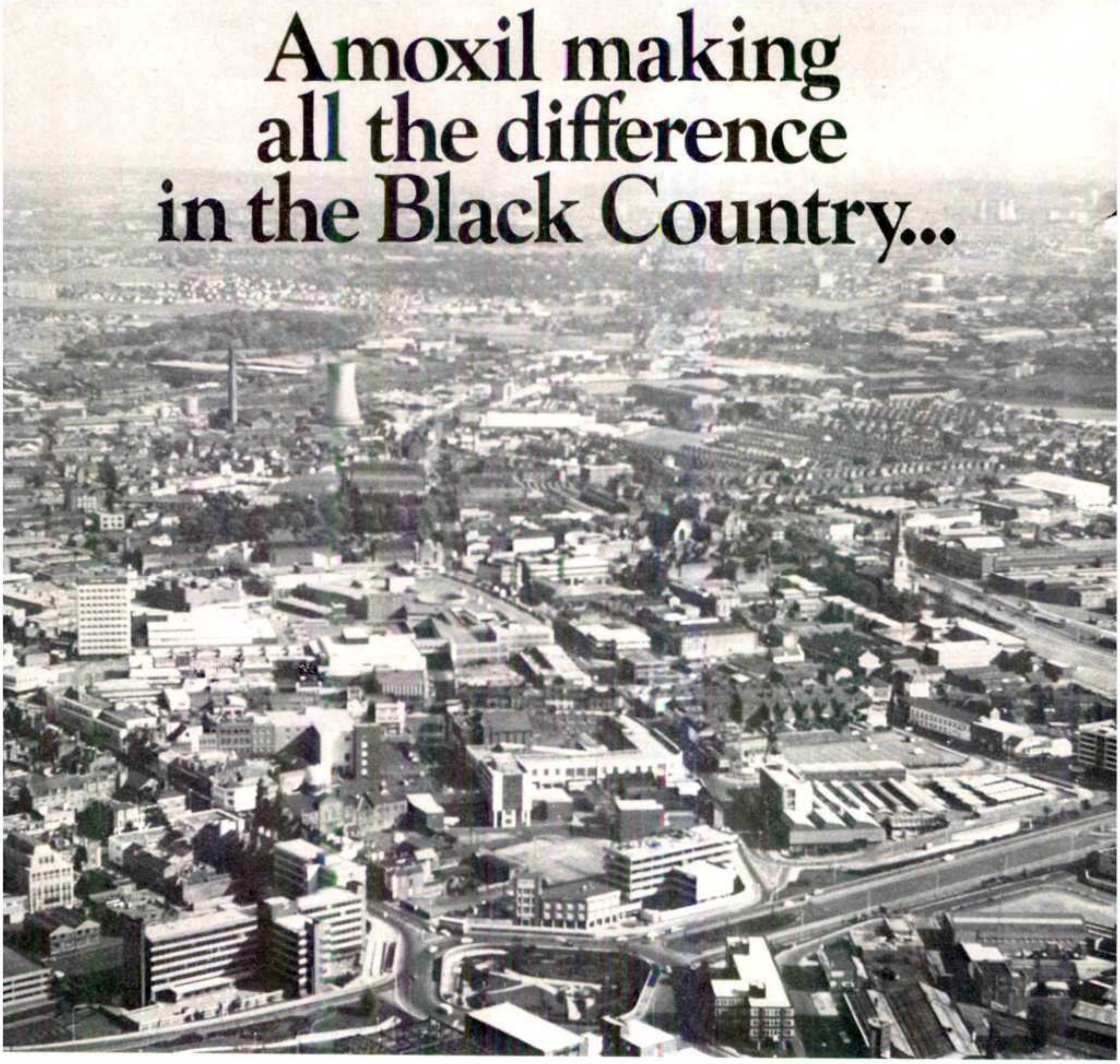

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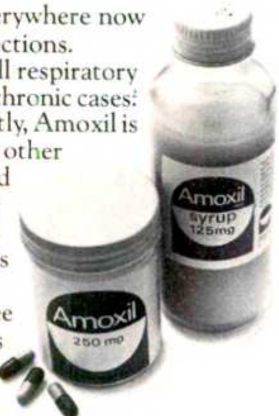

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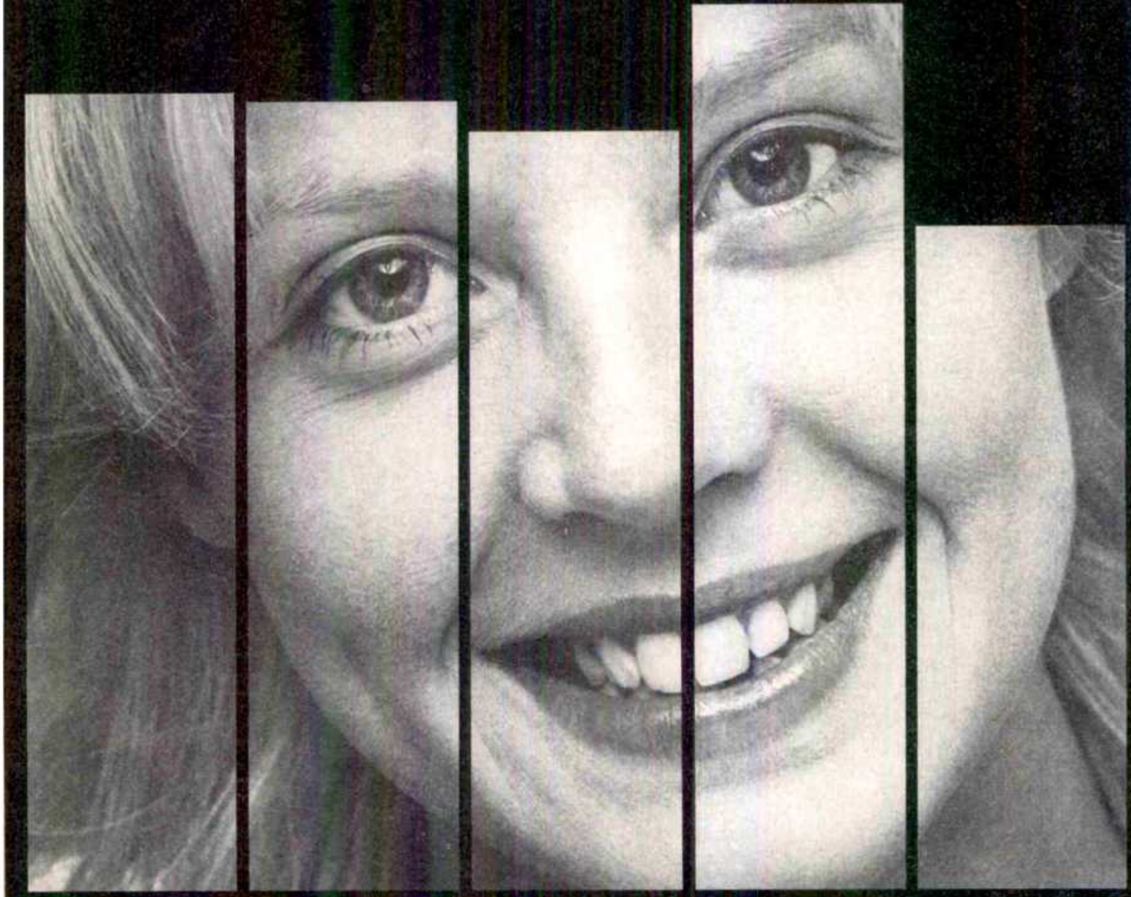

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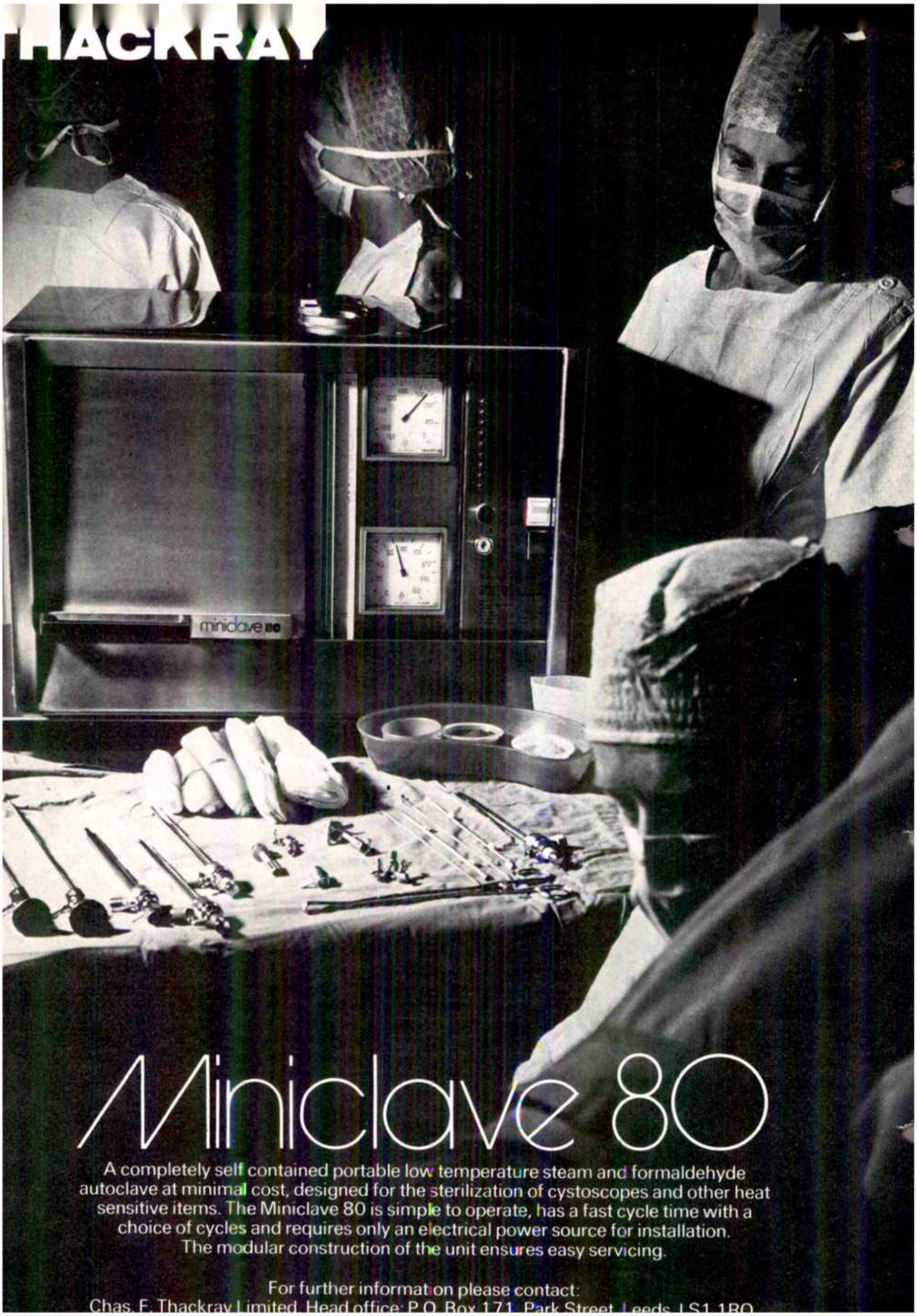

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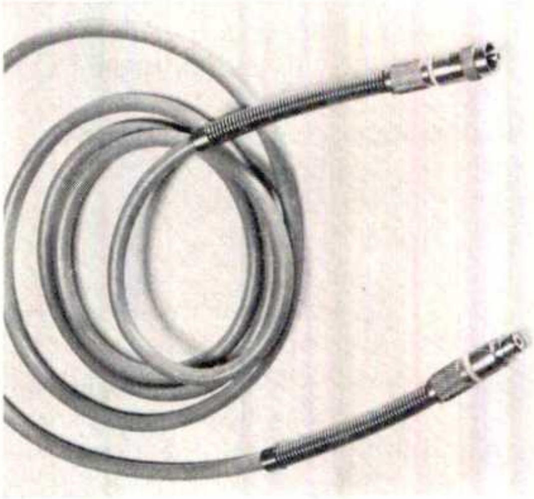

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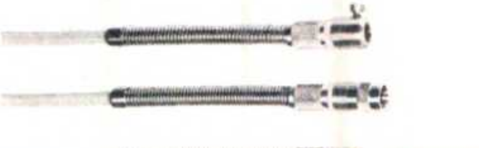

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Constituents of Urinary Calculi containing Struvite

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Department of Chemistry, University College, London

Struvite (magnesium ammonium phosphate hexahydrate) usually with carbonate-apatite, are the constituents of urinary calculi associated with infection of the urine by urea-splitting organisms. It has been stated that once they are deposited in a stone, further layers will be composed of them and any change in composition is rare. As long ago as 1825, Prout said that mixed phosphates were not followed by other depositions and there were few exceptions to the rule, and in 1963, Prien reported that statistically the exception was only 1 in about 2,300 calculi in which struvite appeared.

In our study of the composition of urinary calculi, a number of stones have been found in which either struvite was not deposited to the surface or other compounds were present with struvite, after a marked deposition of this material in the preceding layer or layers.

Material and Methods

The crystalline composition of 2,533 urinary stones has been determined by the X-ray powder method (Lonsdale, Sutor and Wooley, 1968). By cutting the calculi carefully in half and analysing samples from the different layers when possible, the sequential deposition of the crystalline constituents from the nucleus to the surface was determined in 1,889. The collection analysed is comprised of upper and lower urinary tract stones from children and adults in industrialised and technically-developing countries, and of bladder stones from museum collections. It is therefore representative of the different types of urolithiasis known (Sutor, Wooley and Illingworth, 1974).

Results

Out of the 715 stones in which struvite was present, the sequential deposition of the crystalline constituents could be determined in 615. In 139 of these, other constituents followed a marked deposition of struvite. In 122, the compound was accompanied by struvite; in 16, it replaced struvite; and in 1, both types of deposition had occurred (Tables I and II). Excluding the apatites, one or both of which usually occur with struvite, all constituents of urinary calculi found in our work (Sutor, Wooley and Illingworth, 1974) could accompany struvite. More often than not, the substance had also been deposited in the inner layers (Table I). Ammonium acid urate and the mono- and di-hydrates of calcium oxalate were the most commonly found compounds in this category. All the constituents of urinary calculi, except uric acid dihydrate, sodium acid urate monohydrate, cystine and brushite have been found to completely replace struvite in a stone (Table II). Calcium oxalate monohydrate was the most frequently occurring compound in this group.

Discussion

The study shows that in urinary calculi, compounds are frequently deposited after struvite, and these compounds can either accompany struvite or completely replace it in subsequent layers. This has occurred in all types of stones included in this survey, namely upper and lower urinary tract calculi from adults and children in technically-developing and industrialised countries and bladder stones in museum collections. The compounds usually involved are the most common constituents of stones apart from ammonium acid urate. The frequent occurrence of this material probably results from its formation in urine both infected by urea-splitting organisms and supersaturated with uric acid (Teotia and Sutor, 1971).

The formation of struvite in human urinary calculi has not been thoroughly investigated. It is taken as being indicative of infection by urea-splitting organisms but whether it can occur in

Table I

Number of Times a Compound followed Struvite, and was accompanied by Struvite in that Layer, for a Group of 615 Stones containing Struvite. Usual Type indicates the Compound had been Present in a Previous Layer, Italics indicates no Occurrence in Previous Layer.

Constituent	Group 1		Group 2		Group 3		Group 4		Unclassified		Total	
Anhydrous uric acid	1	...	1	...	...	...	...	...	...	...	2	...
Uric acid dihydrate	...	...	1	...	...	...	...	...	...	...	1	...
Ammonium acid urate	20	*1*	9	...	1	*1*	10	*2*	24	*3*	64	*7*
Sodium acid urate monohydrate	...	...	...	...	...	...	1	...	...	*1*	1	*1*
Calcium oxalate monohydrate	10	*3*	2	...	5	*6*	2	*1*	18	*4*	37	*14*
Calcium oxalate dihydrate	5	*4*	...	*2*	4	*4*	...	*1*	3	*3*	12	*14*
Cystine	...	...	...	...	1	..	...	...	...	...	1	...
Brushite	...	*1*	...	...	...	..	...	*1*	...	*1*	...	*3*
Whitlockite	1	...	...	...	1	*1*	1	...	1	...	4	*1*
Octacalcium phosphate	...	...	...	...	...	..	1	*2*	...	...	1	*2*
Unidentified material	...	...	...	...	1	*1*	...	...	...	...	1	*1*
Number of stones in each group	32		11		21		19		40		123	

Group 1 = Children's bladder and kidney stones from technically-developing countries and children's bladder stones from museum collections.
Group 2 = Adult bladder stones from technically-developing countries and museum collections.
Group 3 = Adult and children's upper urinary tract stones from industrialised countries.
Group 4 = Adult and children's lower urinary tract stones from industrialised countries.

Table II

Number of Times a Compound followed Struvite, but was not accompanied by Struvite in that Layer, for a Group of 615 Stones containing Struvite. Usual Type indicates the Compound had been Present in a Previous Layer, Italics indicates no Occurrence in Previous Layer.

Constituent	Group 1		Group 2		Group 3		Group 4		Unclassified		Total	
Anhydrous uric acid	...	...	...	*2*	...	...	...	*1*	...	...	...	*3*
Ammonium acid urate	...	...	2	...	1	...	1	...	...	...	4	...
Calcium oxalate monohydrate	...	...	3	...	2	*1*	2	...	2	*1*	9	*2*
Calcium oxalate dihydrate	...	...	...	...	...	*2*	...	...	1	...	1	*2*
Whitlockite	...	...	...	...	1	*1*	1	...	...	...	2	*1*
Octacalcium phosphate	...	...	...	...	...	...	1	...	...	...	1	...
Number of stones in each group	0		4		7		3		3		17	

Key to groups in Table I.

sterile urine is not known. As in other studies where the composition of stones containing struvite has been determined, data were not available to assess if the latter situation is possible. However, struvite is the usual constituent of calculi from cats and is formed in non-infected urine (Jackson, 1971). This suggests that, under certain circumstances, struvite might precipitate from non-infected human urine.

Although the conditions under which compounds accompany or replace struvite in stones are not known, this work has shown that the presence of such compounds is not as uncommon as hitherto thought.

Summary

In a collection of 615 stones containing struvite and in which the sequential deposition of the constituents from the nucleus to the surface had been determined, other substances were found to follow a marked deposition of struvite in 139 cases. In 122, the compound was accompanied by struvite, in 16, struvite was replaced by it and in 1, both types of deposition had occurred in different layers. All urinary stone constituents could accompany struvite and many could replace this compound.

This work was financed by the Medical Research Council.

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IgG Catabolism in Anephric Patients

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Normal rates of catabolism of IgG have been reported in both humans (Waldmann, Strober and Mogielnicki, 1972) and mice (Souhami, 1973) with chronic renal failure. In mice, the rate of catabolism of human IgG is unaffected by bilateral nephrectomy (Wochner, Strober and Waldmann, 1967). By contrast, much diminished rates of IgG catabolism have been found in rats following bilateral nephrectomy, although albumin catabolism remains normal (Traux and McCoy, 1965). This observation suggested that the kidney is an important site of IgG catabolism in this species. The clinical use of maintenance haemodialysis provides an opportunity to investigate the effect of severe renal damage and of bilateral nephrectomy upon IgG catabolism in humans.

Patients and Methods

Patients and Controls. 2 normal controls and 5 patients were studied. Informed consent was obtained in each case. Details of the patients are given in Table I. Patients received two 14-hour single pass haemodialyses per week with Kiil dialysers using 8μ cross-grained wet stretched 0·6 m^2 cuprophane membranes. No significant change in body weight or blood pressure occurred in any patient during the period of study.

Preparation of ^{125}I IgG. IgG was prepared from the serum of a normal Australia antigen negative donor. The serum was fractionated on DEAE cellulose, prepared in 0·0175M phosphate buffer pH 6·2. The sample showed a single IgG band on immuno-electrophoresis against sheep anti-whole human serum (Wellcome Laboratories) and no other proteins were detected when the sample was concentrated 8-fold. The sample was sterilised by millipore filtration and stored at −20°C. The final concentration of IgG was 4·48 mg/ml. The sample was pyrogen free when tested on rabbits and no toxic reactions were seen in any study. Iodination with ^{125}I (Radiochemical Centre, Amersham) was carried out under sterile conditions before each study by the iodine monochloride method of McFarlane (1963). The specific activity was approximately 0·5 atoms per molecule.

Table I

Subject	Age/Sex	Diagnosis	Nephrectomy	Duration of Dialysis	Total IgG	T/2 Days
L. R. I. B.	33/M	Normal	No	...	825	19·2
R. L. S.	34/M	Normal	No	...	1240	20·8
L. W.	57/M	CGN	No	1 year	930	21·7
R. C.	38/F	CGN	No	4 years	1300	23·2
A. B.	37/M	CGN	No	1 year	1200	17·2
E. B.	34/F	M/HT	Yes	1 year	1515	19·5
B. E.	36/F	M /HT	Yes	2 years	1800	22

CGN = chronic glomerulonephritis.
M H/T = malignant hypertension.
IgG measured by radial immunodiffusion. Normal range 800 to 1800 mg%.

Each injected sample contained approximately 20 μc of radioactivity and in each case over 97% of the sample was precipitated by 10% trichloracetic acid (TCA).

Catabolism of IgG. The labelled IgG was injected intravenously and the first blood sample taken 15 min after injection. In normal subjects subsequent blood samples were taken at 24-hour intervals for 30 days and all urine was collected over the same period of time. In the patients pre-dialysis blood samples were taken over a period of 4 to 6 weeks. The 3 non-nephrectomised patients produced only very small quantities of urine and no collections were made. Patients and controls took 180 mg potassium iodide daily for 2 days before, and 1 week after the study began.

Each clotted blood sample was separated and the radioactivity in 2 ml of whole serum measured in a Packard gamma counter. The TCA precipitable radioactivity of another 2 ml sample was also measured.

Protein Fractionation. Pre-and post-dialysis blood samples from each patient were fractionated by gel filtration using Sephadex G200 at 4°C. The distribution of radioactivity was then measured. A similar fractionation was carried out on a sample from one control.

Results

Normal values for $T\frac{1}{2}$ were obtained in both controls (Table I). The time for equilibration was normal at 6 to 7 days and thereafter the decay curve followed an exponential course. There was no evidence of denaturation of the labelled IgG in the pattern of early urinary excretion of radioactivity. The $T\frac{1}{2}$ of IgG was also normal in the uraemic non-nephrectomised and anephric patients. A value of $T\frac{1}{2}$ was obtained without difficulty when the study extended over a 6-week period. In each case the catabolism of IgG followed exponential kinetics. Although both whole serum and TCA precipitable radioactivity was measured, free ^{125}I was not detected in pre- or post-dialysis samples in any patient.

Satisfactory separation of pre- and post-dialysis samples was obtained on Sephadex G200 fractionation. The distribution of radioactivity was entirely in the IgG region in all cases and there was no evidence of alteration of molecular size as a result of dialysis. The distribution of radioactivity was identical to that of the original sample when this was added to the patient's serum and fractionated.

Discussion

This study confirms the findings of Waldmann *et al.* (1972) that the catabolism of IgG is normal in uraemic humans and establishes for the first time that the same is true of anephric humans. We cannot exclude the possibility that renal catabolism of IgG occurs in normal humans and that a compensatory increase in catabolism at other sites might obscure the effect of nephrectomy. However, the likely explanation of these observations is that the kidneys play no major role in IgG catabolism. It seems unlikely that any abnormality of IgG catabolism is of significance in the genesis of the altered immunological status of patients with chronic renal failure.

Summary

The catabolism of purified human ^{125}I labelled IgG has been studied in patients with chronic renal failure, both nephrectomised and non-nephrectomised, on intermittent haemodialysis.

In all patients the $T\frac{1}{2}$ of IgG was the same as in normal controls, and using chromatographic separation on Sephadex G200, there was no evidence of alteration of molecular size as a result of dialysis.

The results do not support the notion that the kidney is an important site of IgG catabolism in humans.

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Short Case Report

Giant Tuberculous Hydronephrosis

Only 150 cases of giant hydronephrosis were described till 1968, 87% of which were congenital (Tombari *et al.*, 1968). Tuberculous kidney presenting as giant hydronephrosis is rare (Kollins *et al.*, 1974).

Case Report

A 25-year-old male was admitted for a gradually growing abdominal swelling of 6 months duration and swelling of the entire right lower limb of 3 months duration.

Examination revealed matted upper deep cervical lymph nodes with overlying scars of healed cold abscesses, and uniform swelling of the right lower limb from toes to groin. There was a massive right-sided hydronephrosis of 9″ × 6″ × 7″ size extending right down into the pelvis. Clinically, lungs showed fibrocaseous lesion of the right upper zone. Other systems were normal.

ESR was 103 mm, AFB could be cultured from both urine and sputum, chest radiograph confirmed fibrocaseous lesion in the right upper zone. Plain X-ray KUB and IVP (Fig.) revealed a massive right-sided hydronephrosis and a normal left kidney. Cystoscopy showed tuberculous ulceration around the right orifice.

Right nephrectomy was performed after a preliminary nephrostomy. Kidney contained 3,500 cc of serous fluid and showed tuberculous lesion histologically.

The swelling of the right lower limb disappeared after draining the kidney.

Comment

Compression of ipsilateral iliac vein by giant tuberculous hydronephrosis producing unilateral lower limb oedema, which disappeared after treatment, has not been recorded in the literature, though oedema of the lower limbs was described with distended bladder (Yang and Mitchell, 1968), pelvic tumours and hydrocolpos.

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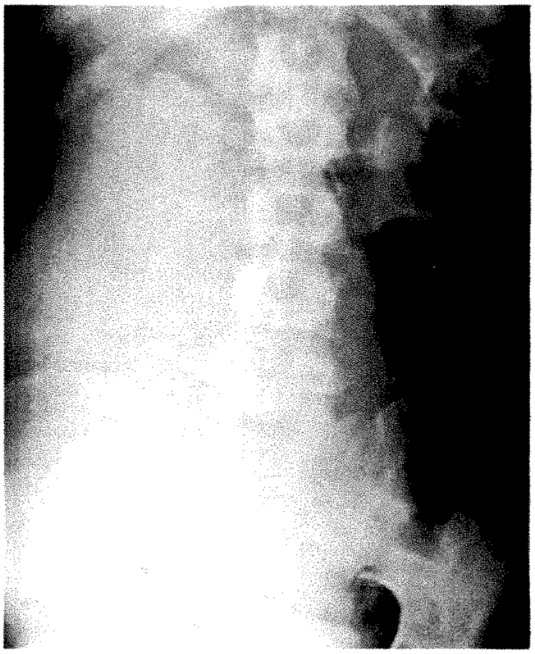

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Grey-scale Ultrasound Imaging: Assessment of Acute Hydronephrosis

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The renal anatomy may change rapidly during the development and resolution of an acute hydronephrosis, so that repeated imaging procedures may be required. One intravenous pyelogram (IVP) is required to localise the site of the obstruction but the ionising radiation hazard limits the number of examinations. In such situations, ultrasound is especially attractive as a non-ionising radiation which permits multiple examinations. We report here 3 patients who developed acute hydronephrosis after an intravenous pyelogram under conditions in which further radiological contrast procedures would have been undesirable or technically difficult. In each case, the use of grey-scale ultrasonography permitted an accurate diagnosis to be rapidly made.

The equipment used here was a custom-built grey-scale machine (Taylor, Carpenter and McCready, 1973) but machines of similar potential are becoming commercially available. The scanning techniques for visualising the kidneys have been described (Taylor and Hill, 1975) and result in displaying the anatomy as shown in Figures 1b and 2b.

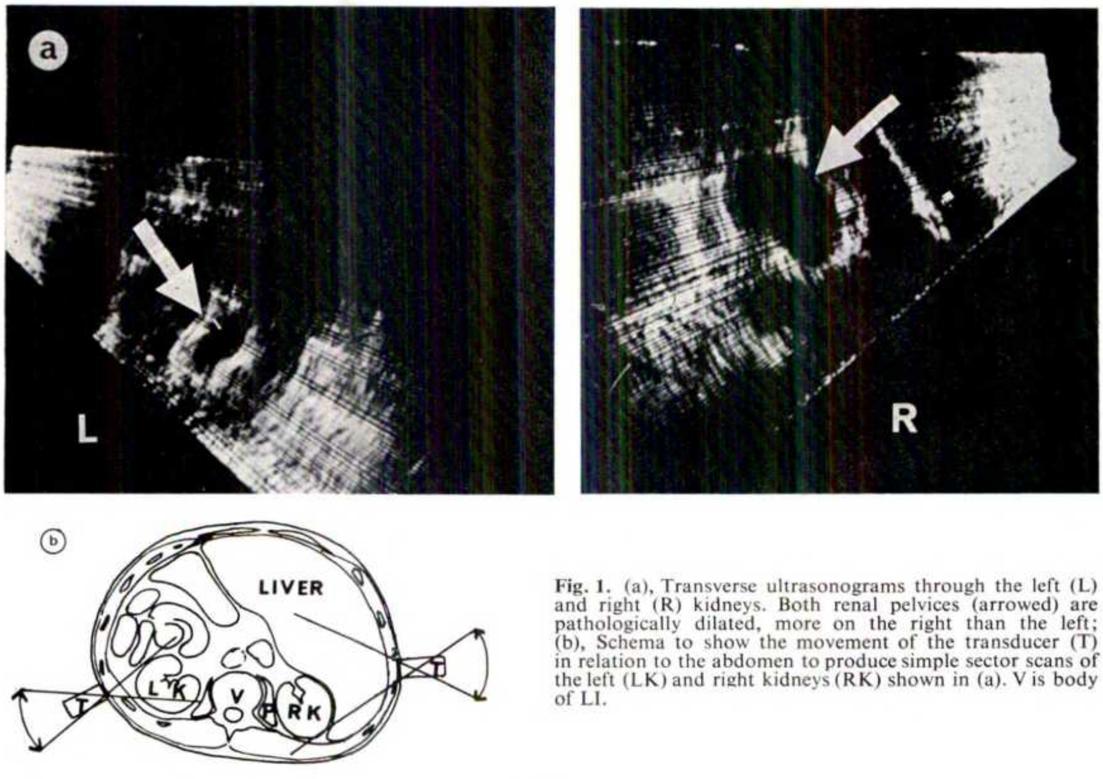

Fig. 1. (a), Transverse ultrasonograms through the left (L) and right (R) kidneys. Both renal pelvices (arrowed) are pathologically dilated, more on the right than the left; (b), Schema to show the movement of the transducer (T) in relation to the abdomen to produce simple sector scans of the left (LK) and right kidneys (RK) shown in (a). V is body of L1.

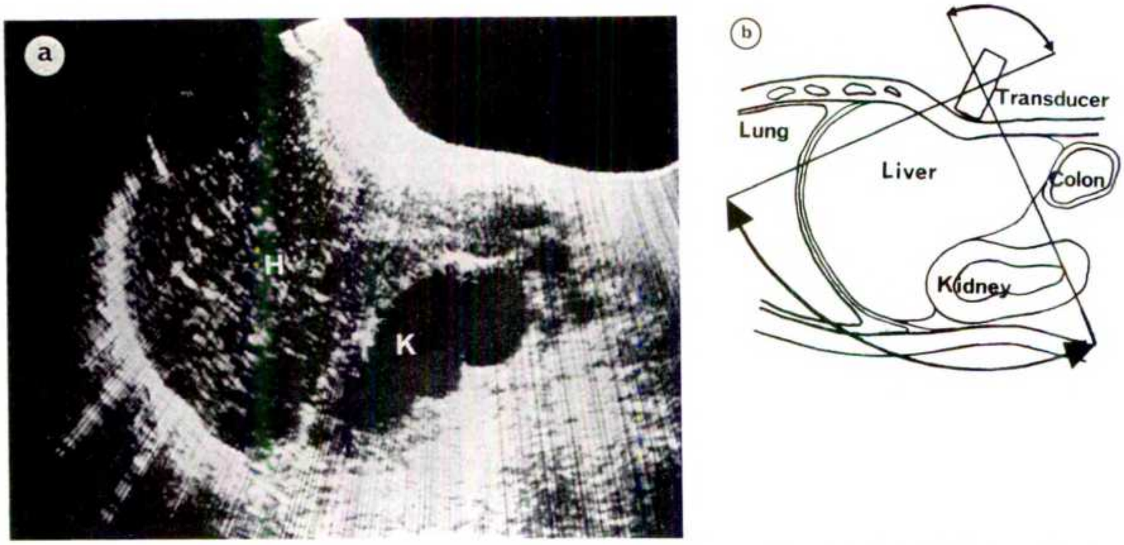

Fig. 2. (a), Parasagittal ultrasonogram through the right lobe of the liver (H) and right kidney (K). The kidney is replaced by gross hydronephrosis; (b), Schema to show the movement of the transducer and displayed anatomy shown in (a).

Case Reports

Case 1

A 64-year old woman presented with a short history of post-menopausal bleeding and E.U.A. revealed an extensive carcinoma of the cervix which obliterated the fornices and extended through the parametrial tissues to the side walls of the pelvis. Histological examination showed a poorly differentiated squamous cell carcinoma. An IVP was normal despite extensive pelvic and para-aortic lymph node involvement shown by lymphography. Whole pelvic irradiation was carried out giving 5,000 rads in 36 days. 1 week after completion of her treatment the patient was admitted as an emergency in a semi-comatose state with a blood urea of 250 mg % (42 mmol/l). Her condition deteriorated and she became anuric. An ultrasound examination was requested to determine the cause of her renal failure. During the examination the patient was confused and restless and commenced grand mal convulsions. Despite this, the examination was rapidly completed while appropriate anticonvulsant therapy was instituted. The ultrasonogram (Fig. 1a) shows a transverse tomogram through both kidneys. There is marked dilatation of both renal pelves (arrowed) but this is more marked on the right. The plane of the sections and the method of scanning is shown schematically in Figure 1b. Surgical intervention was considered but deferred because of the extent of the disease and the patient died shortly after this. A postmortem examination revealed secondary deposits in the lungs, liver, heart, pancreas, thyroid, adrenals and pelvic soft tissues with extensive involvement of the lymph nodes. Both kidneys showed metastatic nodules and dilated pelves. The left ureter was infiltrated by tumour from the para-aortic lymph nodes but the right ureter traversed the tumour without being microscopically involved by it.

Case 2

A 65-year-old woman presented with post-menopausal bleeding and clinical examination showed a stage III carcinoma of the cervix which was reported as highly anaplastic on histological examination. An IVP showed a left hydronephrosis and a non-functioning right kidney. Whole pelvic irradiation was commenced but after the third treatment, she became anuric and it was found that her blood urea had risen from 70 to 250 mg % (12 to 42 mmol/l). Clinically, this appeared to be due to bilateral post-renal obstruction and an ultrasonogram was carried out to confirm this.

Figure 2a is a parasagittal section taken through the right lobe of the liver and shows a gross degree of hydronephrosis replacing most of the right kidney. The method of scanning and displayed anatomy are shown in Figure 2b The left kidney was also moderately hydronephrotic.

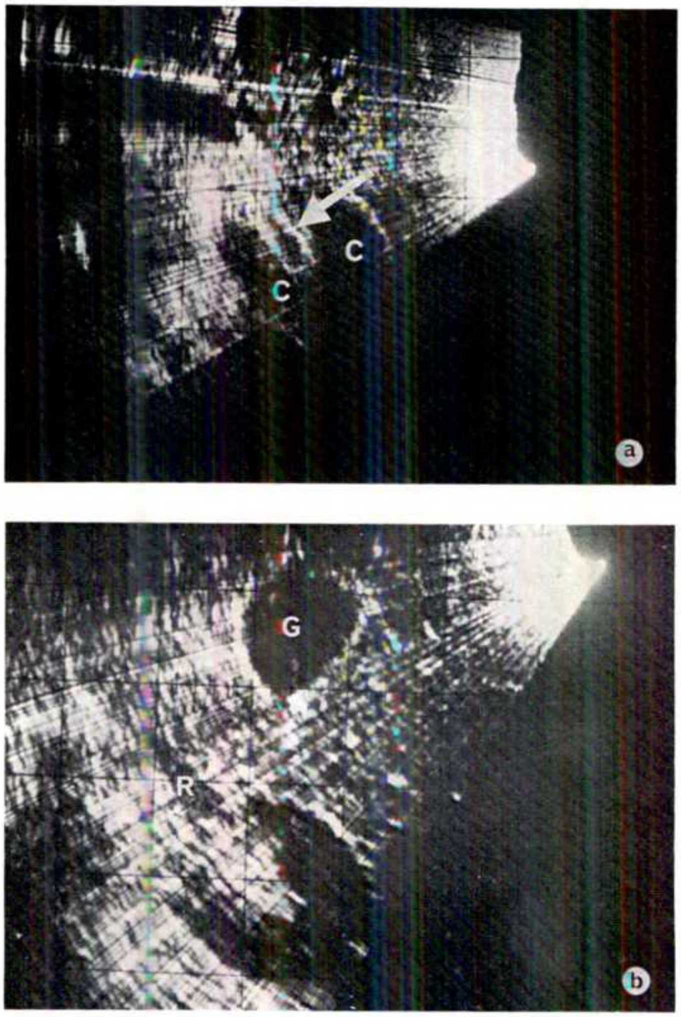

Fig. 3. (a), Transverse ultrasonogram through right kidney showing minimal dilatation of the renal pelvis (arrowed). C is renal cortex; (b), Transverse ultrasonogram through the normal right kidney. R is renal vein and G is gallbladder.

Case 3

A 40-year-old woman presented with a solitary enlarged lymph node in the right groin which histologically proved to be a diffuse, poorly differentiated lymphoma. Routine investigations were normal including an IVP, lymphogram, liver and spleen radio-isotope scan and bone marrow. A staging laparotomy and splenectomy confirmed the clinical impression of Stage 1. Irradiation was commenced to the para-aortic strip, pelvic and inguinal nodes (inverted Y). One month after laparotomy, having received 1,100 rads, the patient developed pain in the right upper abdomen and loin. To determine the cause for this, she was referred for ultrasonic examination of the right kidney. The ultrasonogram showed minimal dilatation of the renal pelvis (Fig. 3a) as compared to the normal seen in Figure 3b. The degree of dilatation increased over the course of 3 days before an IVP was performed (Fig. 4). This showed moderate hydronephrosis of the right kidney and dilatation of the ureter apparently due to an obstruction in the lower ureter near a silver clip (arrowed) which had been left as a marker at laparotomy. The patient's symptoms gradually improved and 4 repeat ultrasonograms at weekly intervals showed a slow return to normal (Fig. 3b) over this period of a month. It thus appeared that the temporary ureteric obstruction was due to a reactive process at the site of the metal clip rather than to any involvement of the ureter itself.

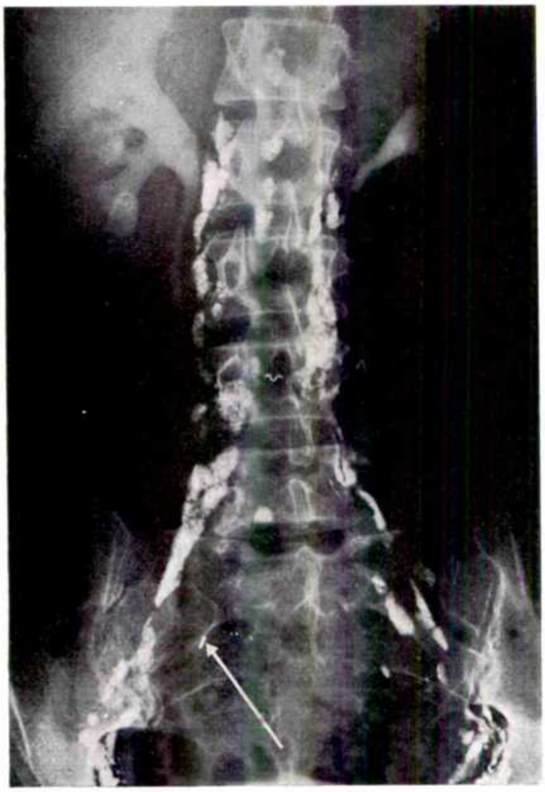

Fig. 4. IVP at 35 min after injection. There is a moderate degree of hydronephrosis of the right kidney with dilatation of the right ureter as far as the region of a silver clip (arrowed).

Discussion

These 3 patients demonstrate the practical value of a diagnostic ultrasound facility in the management of cancer patients. However, the results are even more applicable to other groups of patients, especially young people with chronic renal disease in whom repeated radiological examinations involve an undesirable ionising radiation hazard.

In cases 1 and 2, the high blood urea would have made even high dose urography difficult but the confused, restless and convulsing condition of the patients made this impracticable. In contrast, the ultrasound examination was completed in less than 5 min and adequate resolution was achieved despite lack of patient co-operation.

In case 3, there was some reticence to repeat an IVP examination only 3 weeks after a normal one without prior use of ultrasound to justify it. After the ultrasound examination, the IVP was of course required to localise the site of the obstruction. Thereafter, ultrasound was of value for repeated examinations to monitor the return to normal.

Renography has great attractions as a simple technique to assess renal function, but ultrasound is complementary to display the anatomy and pathology. Ultrasound is particularly successful in differentiating between cystic and solid space-occupying renal lesions and may preempt the need for renal arteriography. The recent developments of improved technology and modified scanning techniques have greatly improved the resolution and hence increased the applications for diagnostic ultrasound in renal disease.

Summary

Rapid changes in the renal anatomy during the development and resolution of an acute hydronephrosis may require multiple imaging procedures. The ionising radiation hazard limits the extent to which this may be achieved by intravenous pyelography. Grey-scale ultrasound offers a safe, non-intrusive technique for visualising the renal pelvis which may be repeated daily. The value of such an ultrasound facility is illustrated by 3 case histories.

We thank Dr J. Baker and Professor M. J. Peckham for permission to publish these case histories.

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Nephroscopy[1]

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Few urologists would operate upon a bladder without looking inside it first but how many will look inside a kidney?

This is the radiograph (Fig. 1) of a kidney exposed at operation. Many stones have already been removed, but this one small opacity remains. The surgeon is confronted with two problems. The first, what is the exact spatial position of that opacity? The second, is it a stone in the collecting system or calcification in the renal parenchyma? Although lateral X-rays or an operative pyelogram may help, it is difficult radiologically to be sure of the answer to either problem. On the other hand nephroscopy, the inspection of the interior of the kidney, might give the answer to both.

In nephroscopy the instrument is usually introduced through a pyelotomy to inspect the pelvis and the calyces of the kidney. This procedure is rather like performing cystoscopy on a bladder containing multiple diverticula and trying to examine the interior of each diverticulum. It can be done, but it is not easy. Alternatively, the instrument may be introduced through a nephrotomy into a calyx, when only that calyx and the pelvis can be examined. This method is particularly applicable after nephrolithotomy to make sure the calyx has been cleared of stone completely. In the first report of nephroscopy (Rupel and Brown, 1941), a panendoscope was ingeniously introduced into the kidney along a nephrostomy track by threading its sheath over the nephrostomy catheter which was then removed. The stone was seen with the panendoscope and was removed with Lowsley's forceps.

Over the last year I have been trying out various ways of performing nephroscopy and various instruments and the ones I have used have included the ordinary Storz infant panendoscope (Fig. 2) and the Storz nephroscope (Figs. 3 and 4). Occasionally with hydronephrotic kidneys I have used an adult-size panendoscope.

The actual technique of nephroscopy is remarkably simple. To obtain enough elbow room to work a good exposure is essential and I use the lateral approach through the bed of the last rib with the operating table fully broken. The kidney must be fully mobilised so that it can be rotated in both the horizontal and the vertical axes.

A wide incision is made in the renal pelvis. Some authors have suggested that only a small incision should be used and even that it should be made watertight around the nephroscope with a purse-string suture. This is quite wrong. With good irrigation an excellent view can be obtained even with the pelvis completely opened up, as for example by the incision made in doing a pyeloplasty.

The instrument is then introduced into the pelvis with the irrigation fluid running and is guided on under vision into the major and minor calyces of the kidney, in much the same way as a urethroscope is guided up the urethra under vision. By a combination of manipulation of the instrument and rotation of the kidney, it is often possible to introduce even a straight instrument into all the calyces of the kidney. The upper calyces are the easiest to enter but with suitable rotation of the kidney (it may have to be turned through 180°) it is possible to examine even the lowest calyces.

The irrigation fluid should be run in by gravity as this is always safer than pressure irrigation.

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[1] Presented at the 29th Annual Meeting of the Canadian Urological Association in Ottawa, June 1974.

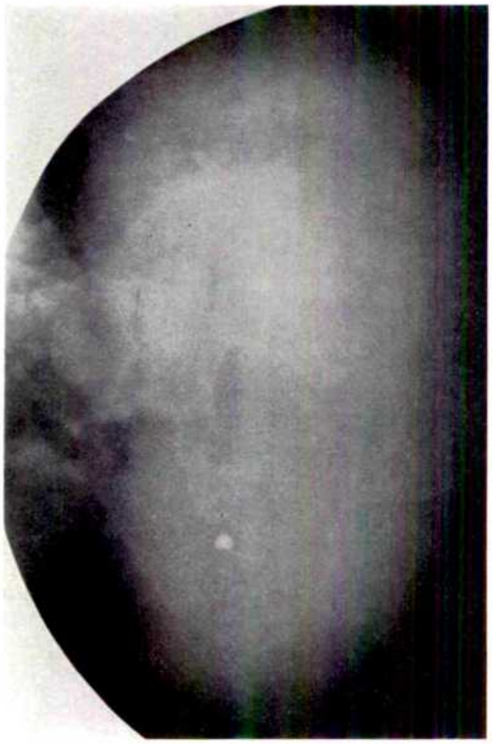

Fig. 1. Radiograph of a kidney exposed at operation showing residual opacity in its lower pole.

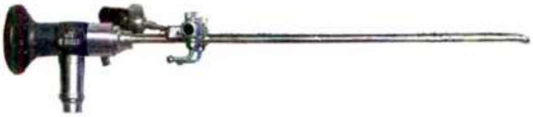

Fig. 2. Storz infant panendoscope.

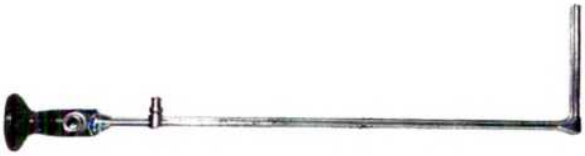

Fig. 3. Storz nephroscope.

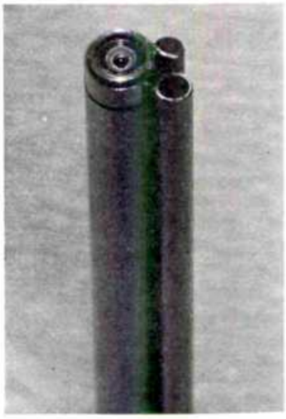

Fig. 4. Tip of Storz nephroscope.

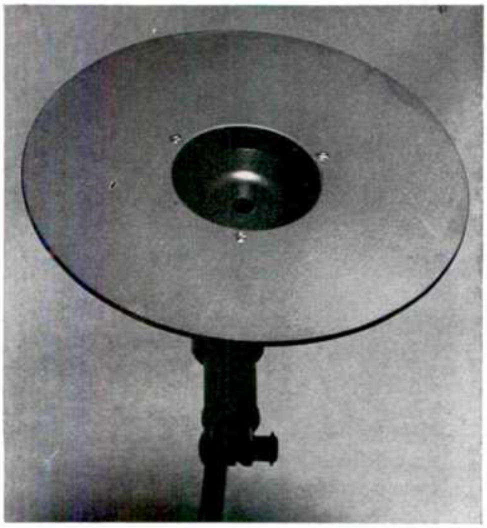

Fig. 5. Sterile shield around eyepiece of Storz nephroscope.

To avoid the risk of introducing infection a special sterile shield (Fig. 5) can be fitted to the eyepiece or the surgeon can don a sterile hood, as described by Trattner (1948). It is probably sufficient, however, to place additional sterile towels around the wound before doing nephroscopy and to discard them immediately afterwards. The surgeon's gown and gloves should also be changed.

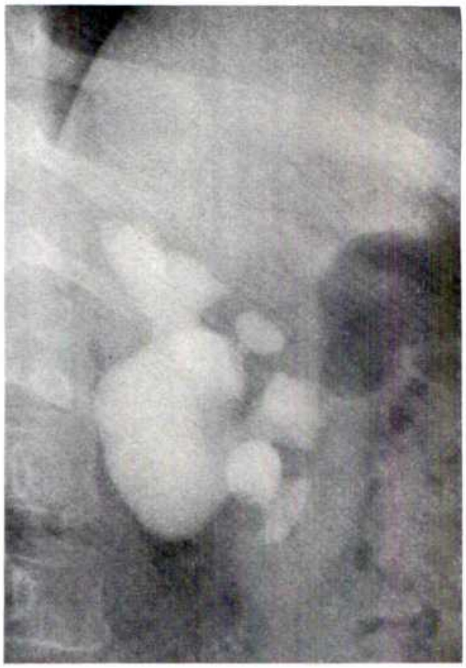

Fig. 6. Intravenous pyelogram of hydronephrotic kidney.

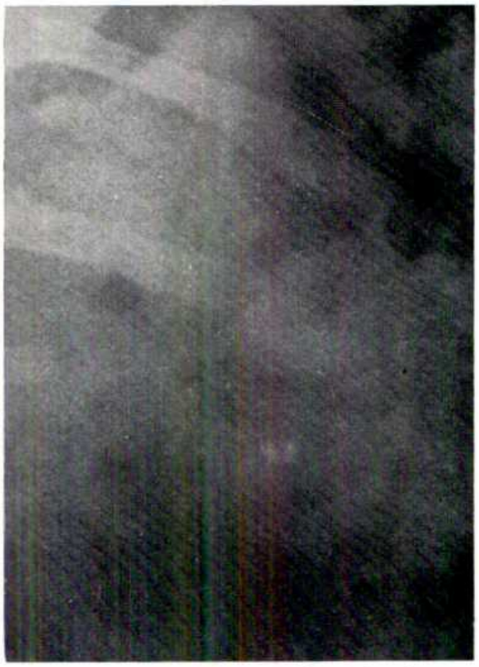

Fig. 7. Plain X-ray of the same kidney showing two small stones in its lower pole.

Comparing the two instruments, the straight Storz infant panendoscope and the right-angled Storz nephroscope, I found the ordinary infant panendoscope to be of greater value. Because of its smaller calibre, 10 Charrière, it can be introduced right into the minor calyces, even of a child's kidney, whereas the wider nephroscope, 16 Charrière, usually sticks in their narrow necks. The advantages of being able to examine a minor calyx completely soon became very apparent. The dome of the pyramid could be examined, as if with a magnifying glass and the fornix all the way around it could be followed. Small particles of stone could sometimes be seen, which were not visible even on the X-ray of the exposed kidney. If all the calyces could be seen to be clear, the check X-ray too was usually clear and, if any calcification was seen on it, this represented calcification in the renal substance, such as a Randall's plaque and not a stone in the collecting system. The position of a stone located with a straight instrument was immediately obvious, so that the panendoscope could be removed, the stone could be grasped easily with straight stone forceps and extracted, whereas the position of a stone located with a right-angled instrument was far less obvious—it had to be worked out.

Figure 6 is the intravenous pyelogram of a hydronephrotic kidney which contained 2 small stones. Figure 7 is the plain X-ray of this kidney taken while the patient was on her way to the operating theatre and shows the stones lying in its lower pole. However, by the time this kidney had been mobilised the stones were no longer in its lower pole. They were easily located with the panendoscope in an upper calyx (Fig. 8) and were removed.

Nephroscopy is still in its infancy and its limitations must be clearly recognised. It is still impossible with the instruments at present available to see into some calyces. If there is much bleeding nothing can be seen. Because of this, the time to perform nephroscopy is before doing any operative procedure on the kidney, not afterwards. I have had no complications from nephroscopy; no kidney was damaged or infected. But obviously it is something which must be done gently and with care.

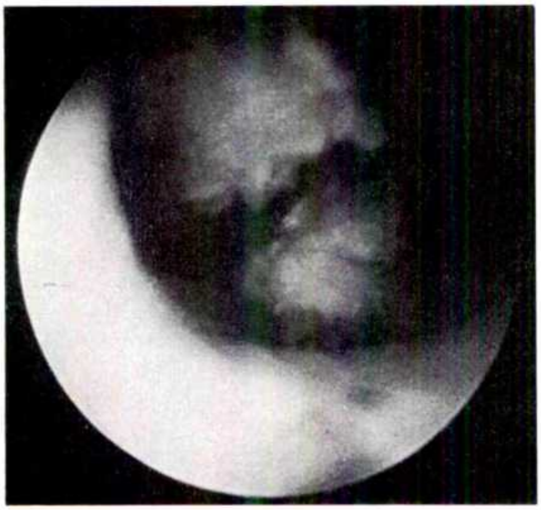

Fig. 8. The same stones in an upper calyx.

What is the future of nephroscopy? The design of the instruments can be improved. For example, I would like to see a narrower Storz nephroscope, size 10 instead of 16 Charrière, with a shorter right-angled limb, 2·5 cm instead of 4 or 6 cm. Flexible fibreoptic instruments offer great promise. The Olympus kidney fibrescope, which is narrow enough to be passed up the ureter and into the kidney is expensive, easily broken and, because of its fine calibre, the view through it is limited. On the other hand, the Olympus fibrescope for bronchoscopy can be used as a nephroscope (Stuart, 1974) and its flexible, controllable tip would seem ideal for manoeuvring into calyces. The Storz nephroscope already has operating attachments and perhaps we can look forward to the development of renal lithotrites and resectoscopes.

Although much still needs to be done to improve the design of the nephroscope, nephroscopy will give valuable information often enough to be able to say it has progressed to being a worthwhile procedure.

Summary

Nephroscopy is a simple and valuable procedure, which may be used to differentiate between stones within the calyces of the kidney and calcification in the pyramids and to locate stones and stone fragments.

The ordinary infant panendoscope is a suitable instrument to use.

Rimmer Bros. kindly lent me a Storz nephroscope to try out. The photographs were prepared by the Department of Medical Photography at the General Infirmary, Leeds. I would like to thank these kind people for their help.

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Ileal Urinary Diversion in Patients with Renal Transplants

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Urinary diversion is rarely used in kidney transplantation patients. Indeed, apart from the paper by Kelly, Merkel and Markland (1966) describing its use in patients with urological complications following kidney transplantation, and the paper by Markland *et al.* (1972) who used the technique when kidney transplantation was carried out in patients with abnormalities of the outflow tract, no other references to the subject can be found in the *Index Medicus* for the years 1963 to 1973. For this reason we report our experience of the use of ileal segments on 8 occasions in 7 kidney transplantation patients.

In 2 of the patients the diversion had been carried out long before renal failure developed and the ureters were implanted into pre-existing ileal conduits (cases 1 and 2). In 3 there were significant abnormalities of the urinary outflow tract at the time definitive surgical treatment for their chronic renal failure was contemplated and ileal loops were constructed as planned procedures before kidney transplantation (cases 3, 4 and 5): in fact 2 separate cadaver kidney transplants and 3 uretero-ileostomies were carried out in 1 of these patients (*vide infra*). In the remaining 2 patients uretero-ileostomies were carried out for urological complications after kidney transplantation (cases 6 and 7).

In 5 instances the ileal stomas were sited in the left iliac fossa and the relevant subsequent kidney transplantations were into the right iliac fossa. In 3 instances the stomas were sited in the right iliac fossa and the relevant subsequent kidney transplantations were into the left iliac fossa on 2 occasions but a second kidney transplant in 1 case was into the right iliac fossa, the same side as the ileal loop stoma. The technique used for implanting the ureters into the isolated ileal loop is shown in Figure 1.

Case Reports

Case 1. Mrs I. A. (d.o.b. 5.11.1937) was treated by total cystectomy and bilateral uretero-sigmoid anastomosis for urological tuberculosis and a vesico-vaginal fistula in 1951. 12 years later there was significant deterioration in renal function and the patient was transferred to Hammersmith Hospital where it was decided to implant the ureters into an isolated ileal loop with the stoma sited in the right iliac fossa. Renal function subsequently improved but 6 years later in December 1969 a live donor kidney transplantation with uretero-ileostomy was carried out. The kidney was sited in the left iliac fossa. Now, 5 years after the kidney transplantation, the patient remains well with the serum creatinine 1·1 mg/100 ml.

Case 2. Mrs J. S. (d.o.b., 22.11.1940) was referred to Hammersmith Hospital in December 1971. Her history was complicated but in essence she had suffered from urological tuberculosis which was treated eventually by total cystectomy and an ileal loop. From 1971 to the end of 1972 she was managed by medical measures for severe chronic renal failure but in May 1973 a cadaver kidney transplantation was carried out: the kidney functioned well but after 2 months there was uncontrollable hypertension due to renal artery stenosis in the transplanted kidney. This was treated by a bypass venous graft but secondary haemorrhage occurred 6 days later and the venous graft had thrombosed. Another vein graft was inserted and although culture of the operation wound grew coliforms and *Ps. aeruginosa* (the same organisms that were present in the ileal loop) there was no impairment of wound healing. The second vein graft also thrombosed and a perinephric abscess which grew *Proteus mirabilis* and a Providence species developed. Vascular access for maintenance dialysis was not possible so peritoneal dialysis was resumed

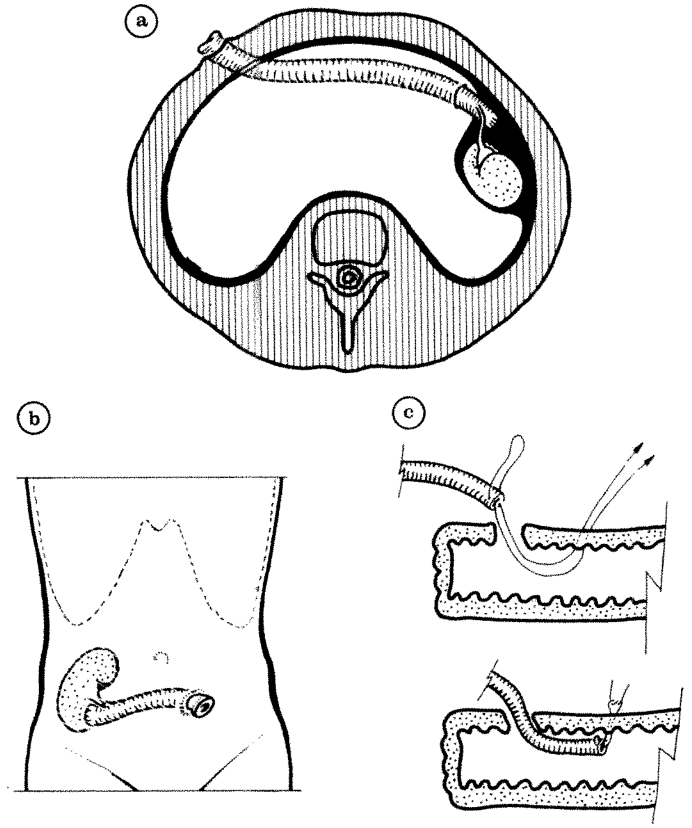

Fig. 1. The technique of uretero-ileostomy in kidney transplantation. The proximal end of the ileal loop is brought through the peritoneum so that the site of the ureteric implantation is extraperitoneal (a). The ureter is implanted into the loop through a 5 mm stab incision and is anchored by a mattress suture (b). The ileal stoma is in the left iliac fossa when the kidney is transplanted to the right side (c).

but she developed *Ps. aeruginosa* and *Staph. albus* septicaemia and died in February 1974, 16 weeks after the transplant nephrectomy. Autopsy showed peritonitis, pulmonary embolism, cerebral and splenic infarction and acute gastric ulceration.

Case 3. Mr J. T. (d.o.b., 15.11.1941) with a post-traumatic neurogenic bladder was transferred to Hammersmith Hospital for haemodialysis and kidney transplantation. In March 1968 an ileal loop was constructed and 18 months later a cadaver kidney transplantation into the left iliac fossa and uretero-ileostomy was carried out. Apart from a mild wound infection with *Ps. aeruginosa* the convalescence was smooth and the function of the transplanted kidney was good. Gradual deterioration of function occurred and the kidney was removed for chronic rejection in October 1971. In August 1972 a second cadaver kidney transplantation was carried out into the right iliac fossa. The operation wound again became infected with *Ps. aeruginosa* (the same organism had persisted in the ileal loop) and there was a urinary fistula from a small zone of necrosis on the anterior surface of the renal cortex. The kidney was wrapped with a large pedicled omental graft and this effectively controlled the urine leak but the patient succumbed 7 weeks after the second kidney transplantation and autopsy confirmed the presence of suppurative pyelonephritis.

Case 4. Mr J. B. (d.o.b., 15.8.1913) with a post-traumatic urethral stricture and chronic renal failure was transferred to Hammersmith Hospital in 1967. As time went on it became increasingly difficult to gain vascular access for haemodialysis so it was decided to undertake kidney transplantation despite the presence of a grossly abnormal bladder with diverticula and a tortuous urethra with false passages and diverticula. An ileal loop was constructed in February 1974 and 6 weeks later a cadaver kidney was transplanted into the right iliac fossa. 3 weeks later the wound was explored for bleeding and the source was an unhealed uretero-ileostomy. *Ps. aeruginosa* and *Proteus sp.* were cultured from the wound. Death occurred 2 days later and autopsy revealed a psoas abscess with breakdown of the ureteric anastomosis and some haemorrhagic ascites.

Case 5. Miss S. C. (d.o.b., 7.1.1943) was treated at the age of 4 years by anterior pelvic exenteration with removal of the symphysis pubis and the external genitalia for Sarcoma botryoides: continuity of the urinary tract was re-established by bilateral uretero-sigmoidostomy. In January 1974 when she had severe renal failure an ileal loop was constituted and a live donor kidney transplant was carried out 2 months later. The internal iliac arteries had been sacrificed at the time of the pelvic exenteration so the arterial anastomosis was end-to-side on to the external iliac artery. The kidney infarcted as a result of renal vein thrombosis and it was removed after 3 days. This was followed 2 weeks later by secondary haemorrhage from a necrotic patch 1 × 0·5 cm on the external iliac artery 2 cm distal to the site of the transplant arterial anastomosis and the external iliac artery had to be ligated above and below the bleeding site. A faecal fistula developed 2 days later and the leg became cold. Thrombectomy was carried out but the circulation in the right leg remained inadequate, the faecal fistula persisted, there was gross infection in the wound, and she died 6 days later. Histology of the necrotic tissue from the site of the bleeding, which eventually led to her death, showed destruction of the arterial wall by suppurative infection and bacteriology of the wound revealed the presence of coliform organisms, *Strep. faecalis* and *Bacteroides*.

Case 6. Miss N. F. (d.o.b., 8.9.1945) had terminal renal failure when she was 21 and was treated by a live donor kidney transplant in July 1966. A urinary fistula developed 4 days later, and despite 4 separate surgical attempts to deal with it in the subsequent 2 months, success was not achieved until an ileal loop with uretero-ileostomy was carried out. Normal micturition was eventually re-established after excision of the distal portion of the loop and anastomosis of the remaining short segment to the bladder. The urine was sequentially infected with haemolytic streptococci (Lancefield Group B), *Proteus sp.* and *Ps. pyocyaneus* and this latter organism subsequently recurred in the bladder urine for approximately 1 year. But now 8 years after the kidney transplantation she is well with a sterile urine and excellent renal function (serum creatinine 0·8 mg/100 ml).

Case 7. Mr J. H. (d.o.b., 10.1.1940) developed severe chronic renal failure and after treatment by regular intermittent haemodialysis for 1 year underwent a cadaver donor kidney transplantation in April 1968. A urinary fistula developed 3 weeks later and exploration revealed avascular necrosis of the lower pole of the kidney and a juxtavesical ureteric stricture. After 2 separate surgical attempts to deal with the fistula had failed, an ileal loop with uretero-ileostomy was carried out. But the urinary leak still persisted and the whole of the anterior surface of the transplanted kidney was exposed in the dehisced wound which was infected with *Ps. aeruginosa*. Despite this the kidney was successfully covered with a large split skin graft (azathioprine therapy had been stopped for some weeks) and 6 months after the kidney transplantation a pedicled omental graft was wrapped around the kidney and the urine leak was finally controlled with all the urine draining through the ileal stoma. When the redundant portion of the ileal loop was resected and the proximal portion, containing the calyceal and ureteric implantations, was joined to the bladder a year after the kidney transplantation, normal micturition was eventually re-established much to the delight of the patient and his nursing and surgical attendants. Now in 1975 he is gainfully employed, the urine is sterile and the serum creatinine is 1·7 mg/100 ml.

Discussion

1 of our 7 patients in whom the ileal loop had been constituted, following total cystectomy 8 years before kidney transplantation, has remained well with good renal function for 5 years. Another, with a neurogenic bladder, in whom the loop was constituted 18 months before kidney transplantation, remained well for 18 months until the kidney finally rejected and the patient succumbed 7 weeks after a second cadaveric kidney transplant was carried out. 2 others, in whom the ileal loops were used temporarily to deal with difficult post-transplantation urinary fistulae, still survive in good health and with good renal function 8 years after kidney transplantation.

There were 3 deaths within 2 months and 1 at 9 months after kidney transplantation and implantation of the ureters into ileal loops. In 2 of these cases the loops were prepared definitively for, and within 6 weeks of, kidney transplantation but in the other 2 the loops had been constituted 4 and 5 years respectively before the patients succumbed.

Infection developed in all 4 of the patients who died but, apart from the ileal loops, there were other significant contributory factors in regard to infection and mortality. In 1 (case 2), attempts to treat uncontrollable hypertension due to stenosis of the renal artery of the transplanted kidney by 2 separate vein bypass graft operations failed; the kidney infarcted and the patient developed septicaemia from infection in the peritoneal dialysis which had to be instituted despite the presence of *Proteus sp.* and *Ps. aeruginosa* in the ileal loop. In another (case 3), a zone of necrosis on the anterior surface of the transplanted kidney caused a urinary fistula. In the 2 others (cases 4, 5) there was serious post-transplantation bleeding which required re-operation: in 1 (case 4), the source of the bleeding was an unhealed uretero-ileostomy while in the other (case 5), the bleeding followed removal of an infarcted transplanted kidney (due to venous thrombosis) and emanated from a patch of septic necrosis on the ventral aspect of the external iliac artery. Organisms indistinguishable from those cultured from the ileal loops were found in all 4 patients who died; in the blood stream, the wound, the peritoneal cavity or the transplanted kidney.

In ordinary circumstances a loop constituted from the distal ileum will remain sterile for some days. It would seem rational therefore to construct a loop at the time of kidney transplantation and to prescribe systemic prophylactic antibacterial therapy to cover the period of high steroid dosage after the kidney transplantation, even though the healing of the suture line of the reconstituted bowel (and the uretero-ileostomy) might be impaired. We have not yet done this, but in the light of our own experience and that of Markland *et al.* (1972) we plan to do so in the future. However, if an ileal loop and uretero-ileostomy is required some time after kidney transplantation, when the patient is receiving only low maintenance doses of steroids, the indications for prophylactic antibacterial therapy would seem to be more obscure.

Summary

Ileal urinary diversion has been carried out on 8 occasions in 7/215 kidney transplant patients. In 6 instances the diversion was required either because the bladder had previously been removed or there was gross abnormality of the outflow tract: in 2 it was successfully employed to deal with difficult post-transplantation urinary fistulae.

4 patients died: 3 within 2 months and 1 at 9 months after the operation.

Infection, with organisms indistinguishable from those cultured from the ileal loop, was a common complication and, although there were other significant factors which contributed to the mortality, retrospective consideration suggests that energetic prophylactic antibacterial therapy should be instituted when kidney transplantation with ileal urinary diversion is undertaken.

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The Long-term Management and Social Consequences of Ureterosigmoid Anastomosis

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Ureterosigmoid anastomosis had widespread popularity until 1950 when Ferris and Odel described its biochemical complications and Bricker reported the use of the ileal conduit as an alternative procedure which avoided these. Although ileal conduit is now considered the method of choice of urinary diversion, being widely used in both children (Rickman, 1964; Ray and De Domenico, 1972) and adults (Wallace, 1967; Phillip, 1969; Mogg, 1970), many patients with ureterosigmoid anastomosis still exist.

We report our experience of the long-term follow-up of ureterosigmoid anastomosis patients, during which we were impressed by the social inconvenience often associated with this procedure.

Patients

In the past 7 years 22 patients, who underwent ureterosigmoid anastomosis from 1 to 18 years ago, have been reviewed at regular intervals at a renal clinic. The sex distribution, reason for operation and the present state of these patients are shown (Fig.). 16 patients had the operation following total cystectomy for carcinoma of the bladder, the remaining 6 for various disorders of micturition, including tuberculous cystitis, urethral stricture and neuropathic bladder. The patients' ages at the time of operation ranged from 12 to 72 years (mean 66 years). 11 patients have died at intervals of 16 months to 13 years after operation, those with neoplastic disease usually dying from spread of the original tumour.

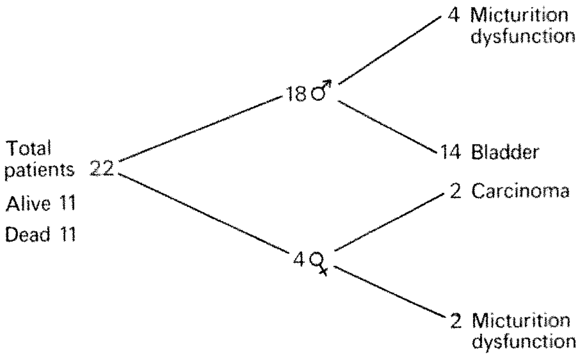

Fig. Ureterosigmoid anastomosis series showing reason for operation.

In the early years patients were referred when they developed biochemical complications but more recently have been seen immediately postoperatively. All ureterosigmoid anastomosis patients were treated with alkali in the form of Shohl's mixture,[1] in daily amounts of 90 to 150 mEq such that the plasma bicarbonate level was maintained between 24 and 28 mEq/l. Capillary pH, base deficit and blood gases were measured routinely at regular out-patient

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[1] Sodium citrate 98 g. Citric acid 60 g.
Amaranth solution BPC 5 ml. Chloroform water and water to 1 litre.

Table I

Occurrence of Urinary Tract Infection, Renal Impairment and Acidosis

Symptomatic UTIs/year		Renal impairment		Acidosis	
Attacks	No. of patients	Serum creatinine at death or May 1974	No. of patients	Episodes	No. of patients
0	9	< 1·0	5	0	13
< 1	6	1·0–1·5	12	1	5*
1	2	1·6–2·0	4	2	3*
2	3	> 2·0	1	3	1*
> 2	2				

* All but one episode occurred prior to alkali therapy.

attendances, to give early warning of poor patient compliance, in taking this therapy. Potassium supplements were not given.

Patients who showed a tendency to recurrent infections were treated with long-term antibiotics, such as cycloserine or cotrimoxazole.

Findings—Complications

Infections

The impracticability of obtaining uncontaminated urine specimens from these patients makes it impossible objectively to prove the presence of infection in the urinary tract. Accordingly patients were repeatedly instructed that all symptoms suggestive of infection must be taken seriously. Shivering, rigors or fever without localising signs outside the urinary tract must be assumed to be due to urinary infection. The majority of patients in our series, 17 of the 22 patients, had less than 2 such episodes per year (Table I). Only 2 patients had more than 2 episodes suggestive of urinary tract infections per year.

Obstructive Uropathy

The detection of deterioration of renal function requires serial plasma creatinine measurements as the blood urea is usually elevated because of colonic absorption of urea and/or ammonia. On occasions when unilateral obstruction was suspected intravenous urography was needed. Renal function as measured by serum creatinine showed little tendency to deteriorate in this series (Table I). 1 patient required nephrectomy for pyelonephritis and another had hydronephrosis of 1 kidney at postmortem. However, during the period of follow-up, only 1 of 22 patients has shown an increase in serum creatinine and this was in a patient with heart failure, within a few weeks of death.

Metabolic Acidosis

In these 22 patients there were 14 admissions for episodes of severe acidosis, usually with hypokalaemia, in 124 patient-years. However 11 of these admissions were before the patients attended our clinic and before being treated with an alkali regimen. 2 further instances occurred in the early years of our experience, when the amount of alkali being given was small. Episodes of acidosis did not occur provided the blood acid-base balance was maintained in the normal range

Table II

Frequency of Bowel Emptying—Number of Bowel Actions During 24 Hours

Time period	0-2	3-5	6-8	> 8
(a)				
Morning	0	10	2	1
Afternoon-Evening	0	1	9	3
Night	4	8	1	0
(b)				
Morning	0	6	0	1
Afternoon-Evening	0	3	2	2
Night	3	3	1	0

(*a*) 13 patients alive in May 1974.

(*b*) 7 patients who had died, and for whom details recorded.

Table III

Ability to Undertake Social Functions

	No Problem	Problematic	Impossible
Shopping	10	3	0
Theatre	10	3	0
Church	6	1	6
Visiting	10	3	0
Bus Travel	4	0	9

by prescribing sufficient alkali as maintenance therapy. Although potassium supplements were not given depletion of total body potassium did not occur using this regimen (Boddy *et al.*, 1975).

Survey of Life Style

We questioned the 11 patients still alive and attending our clinic and also 2 others recently referred from other sources, 1 of whom had had the operation for bladder exstrophy, 38 years previously and the other for sarcoma of vagina 4 years previously. The survey thus includes 13 patients, of whom 10 were male and whose ages varied from 21 to 67 years. Their experience of life with ureterosigmoid anastomosis totalled 105 patient-years and all had had the procedure carried out at least 1 year before the survey.

(a) *Frequency of Bowel Emptying*

Most of the patients had to empty their bowels at unduly frequent intervals. Frequent voiding has been advocated to minimise the biochemical complication but it became obvious the maximum voluntary retention time was often appreciably less than that which was socially convenient. During the daytime most of our patients had to empty their bowels every 1 to 2 hours. 3 of the 13 did so more often (Table II (*a*)). At night the same problem continued and only 4 patients did not rise at least 3 times every night. No patient was able to sleep regularly throughout the night and 1 patient had to rise hourly every night. Similar findings had been noted for 7 other patients who had died (Table II (*b*)).

(b) *Anal Incontinence*

Distressing urgency and incontinence remain a problem to 2 patients well after the immediate postoperative period but most patients claimed to be continent all the time. However, 3 patients regularly took precautions both day and night, while 6 others did so only at night, using incontinence pads, polythene sheets and rubber pants.

(c) *Sexual Function*

3 male patients, who had not had total cystectomy at the time of the diversion operation had unimpaired sexual ability. As anticipated all 7 male patients who had total cystectomy as part of the procedure lost their ability to have an erection. We cannot comment adequately on the effect on female patients, as none of the 3 females had sought sexual intercourse postoperatively.

Table IV

Alteration in Physical Wellbeing of Ureterosigmoid Patients

	Yes	No	Occasional
Incontinence	1	9	3
Urgency	1	11	1
Thirst	6	7	0
Diet: modification required	4	9	0
Pass flatus safely	0	11	2
Separate faeces/urine	0	9	4
Normal sexual ability	2	8	

(d) *Social Consequences*

Patients had to plan their day around the need to pass urine/faeces so frequently. In effect they had to carry a "mental map" of the available toilets in their area and most were loath to venture into places they did not know, or where access to toilets was difficult, such as church or long bus journeys (Table III). Other leisure activities such as theatre-going, visiting friends or shopping were possible for all patients, though for those patients with marked frequency even these activities tended to be hazardous at times and so they did not undertake them very often.

4 patients, who might have been working, were no longer employed but in only 2 cases could this be said to be a result of the complications of the procedure. The other 9 patients were either fully employed or following an active retirement.

Other effects of the operation noted by patients were thirst in 6, while some patients found certain foods or large meals increased their frequency. All the patients knew from experience they would have extremely disturbed nights after even a few drinks. The simple habit of passing flatus was outside these patients' ability, or at least they did so at their peril. On the whole they could not pass urine and faeces separately (Table IV).

Discussion

In the long term, upper urinary tract infections are reported to be common after ureterosigmoid anastomosis (Williams, Burkholder and Goodwin, 1969; Phillip, 1969; Fowler and Wilson, 1973). Back pressure effects and the associated infections may result in deterioration of renal function. The third major complication reported is the so-called hyperchloraemic acidosis which most patients with ureterosigmoid anastomosis develop to some degree (Jacobs, 1967).

Hyperchloraemic acidosis has been held to occur because the colonic urinary reservoir has differential reabsorptive capabilities for some of the ions in the urine. The exact mechanism by which the acidosis develops remains controversial, but seems more likely to be due to colonic secretion of bicarbonate (Wrong, 1970). Investigations carried out in this Unit support this conclusion (unpublished data). The acidosis may or may not be accompanied by hypokalaemia but when present hypokalaemia is invariably preceded by acidosis. It is the long-term morbidity and mortality, resulting from these 3 recognised complications (recurrent infections, obstructive uropathy and metabolic acidosis) which have caused the loss of popularity of this operation.

However, it has proved possible to minimise these complications, and we have found that with adequate alkali therapy, careful instruction of the patient and regular long-term follow-up, none of them is troublesome. Our experience agrees with Fowler and Wilson (1973) that the recognised complications of ureterosigmoid anastomosis are usually controllable.

From the patient's viewpoint ureterosigmoid anastomosis has one major advantage over other methods of urinary diversion. Prospectively at least it seems to offer the possibility of voluntary control of both urine and faeces without a prosthesis. This consideration weighs heavily with the patient and often with the surgeon.

However the quality of life experienced by patients with ureterosigmoid anastomosis has received little mention in the literature. Jacobs and Stirling (1952) in their review of the late results only recorded whether the patients were working or not. Thus of 205 patients surviving more than 3 years, 130 were at work and 36 at school or retired, giving 81% considered active. Pyrah (1956) noted that 18 of 20 patients were in good health, fit and active but commented that a few had adopted certain dietetic restrictions. Such analysis gives no idea of how patients managed on a day-to-day basis. Fowler and Wilson (1973) in reviewing 46 patients who had undergone the operation for carcinoma of the bladder stated that all 28 male and all but 3 of the 12 female patients alive at review had regained full continence and had no diurnal or nocturnal frequency or leakage. Hellström (1952) however, reported that of 50 patients alive 1 year post-operatively, 14 (28%) were partly or completely incontinent. Our experience suggests that most patients do have severe continuing problems, mainly what we consider excessive diurnal and nocturnal frequency. Paradoxically the patients are often uncomplaining, perhaps because they have usually required the procedure because of major neoplastic disease and are grateful to survive.

The choice of method for urinary diversion must take account of several considerations. Many feel that there are few or no indications for ureterosigmoid anastomosis in childhood (Rickham, 1964; Kendall and Karafin, 1973; Megalli and Latimer, 1973). For patients with neoplastic disease some consider that the objective of a continent existence favours ureterosigmoid anastomosis over ileal conduit (Fowler and Wilson, 1973). Others consider that a conduit which is amenable to nursing care is preferable (Wallace, 1967). Ong and Leong (1972) found ureterosigmoid anastomosis unsatisfactory in neoplastic disease and others no longer use it (Pearse, Pappas and Hodges, 1973) or employ it only in patients considered likely to die within a year (Pyrah, 1956; Riches, 1967).

In our experience although the prevalence of medical complications with ureterosigmoid anastomosis can be reduced to a large degree, the operation does not guarantee complete continence and it often gives rise to a restricted life style because of diurnal and nocturnal frequency. These social consequences are major factors in selecting ileal conduit as the more satisfactory means of urinary diversion. Full explanation to the patient of the likely consequences, prior to surgery might well dispel much of the understandable initial patient-preference for ureterosigmoid anastomosis. In those patients in whom the operation is still considered desirable, there is good reason that proof of their ability to retain 6 to 8 oz of fluid in their rectum for at least 2 hours while active, should be obtained, before undertaking ureterosigmoid anastomosis (Phillip, 1969).

Summary

It is regrettable that while the recognised complications of ureterosigmoid anastomosis—recurrent urinary tract infection, and acidosis—can be avoided and obstructive uropathy can be recognised early and so treated, the operation frequently condemns the patient to a restricted life with an unpleasant ritual of bowel frequency and incontinence. It seems that the lack of awareness of this bizarre life-style and the occasional true successes have allowed the operation to remain in use.

Our experience confirms the unpredictability of the end result of ureterosigmoid anastomosis and suggests that the operation should be largely abandoned, in favour of the conduit type procedure.

We wish to thank our surgical colleagues for referring their ureterosigmoid anastomosis patients for long-term follow-up at the Renal Clinic.

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Transperitoneal Ureterolithotomy

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The transperitoneal approach to the ureters for ureterolithotomy has been commended by a number of authors and notably by Qvist, Jaber Muhsen and Al-Waidh (1962). They drew attention to the following advantages enjoyed by this technique.

1. The transperitoneal approach is quicker, easier and less traumatic than the retroperitoneal approach.
2. Incisional herniae are less common following operations on the lower anterior abdominal wall than on the postero-lateral area.
3. The stone can be located immediately on opening the peritoneum and its position maintained by digital control.
4. Removal of the stone involves minimal dissection and mobilisation so that haematoma formation and devascularisation of the ureter is minimal.
5. The transperitoneal approach is easier than the retroperitoneal approach for recurrent calculi.
6. Multiple stones can be removed without extensive mobilisation of the ureter, if necessary by separate ureterotomy incisions.
7. Bilateral ureterolithotomy can be performed through one abdominal incision.

In addition the authors claimed that the transperitoneal operation is safer than the extraperitoneal procedure. They argued that the defensive ability of the peritoneum far exceeds that of the extraperitoneal tissues in relationship to infection and they specifically advised that, after removal of the stone from the ureter, the peritoneal incision over the ureter should not be sutured but the peritoneal cavity drained. In this respect the authors' advice is contrary to that of Michalowski and Modelski (1958), who urged the importance of retroperitoneal drainage if the risks associated with urinary extravasation and infection are to be prevented. So satisfied were Qvist and his colleagues with their results in 22 patients that they recommended the transperitoneal approach in all cases where the stone lay in the juxtaperitoneal part of the ureter and employed it in operations on the abdominal as well as the pelvic ureter.

Material

We have examined the records of all ureterolithotomies carried out in the Urological Department of Coventry from 1967 to 1975 with special reference to the incidence of postoperative complications. The cases have been divided into 2 groups according to the position of the stone in the abdominal or pelvic parts of the ureter.

Results

There were 84 ureterolithotomies performed during this period. Unlike Qvist and his colleagues all the operations on the abdominal ureter were by the traditional extraperitoneal method but the majority of those carried out in the lower third were by the transperitoneal approach.

Table I

			Complications				
			Minor		Major		
Site of stone	Surgical approach	No. of cases	Wound infection	Transient ileus	Severe ileus	General peritonitis	Other
Abdominal ureter	Extraperitoneal	41	6	..	..	..	2 (pulmonary embolism)
Pelvic ureter	Transperitoneal with drainage across peritoneum	16	1	1	1	2	..
	Transperitoneal with extraperitoneal drainage	20	1	2	..	..	..
	Extraperitoneal	3	..	..	..	..	..
	Transvesical	4	..	..	..	..	..
		84					

It is clear that the extraperitoneal approach to the upper two-thirds of the ureter is very satisfactory. Of 41 patients, 2 suffered pulmonary embolism in the postoperative period but 1 was under treatment for carcinoma of the prostate while the other had recently undergone a prolonged period of in-patient treatment for deep vein thrombosis. Both made good recoveries and there is no reason to relate these complications to the type of surgical approach employed. The remaining patients had an uninterrupted convalescence, the only complications being from a minor degree of wound infection in 6 cases. The transperitoneal approach was employed in nearly all cases where the stone lay in the pelvic portion of the ureter. In the first 16 cases, the technique recommended by Qvist and his colleagues—namely, non-suture of the peritoneum over the ureter and intraperitoneal drainage—was employed. The results were less than satisfactory. 3 of the 16 patients had serious postoperative complications, 1 of whom suffered severe ileus, while 2 others developed general peritonitis requiring abdominal exploration.

Case Report

Mr R. S. H., aged 72

This patient attended in April 1971 with right renal colic. 12 years previously a bladder stone had been removed, and 2 years later he passed a stone following an attack of left renal colic. His blood pressure was 160/100 but otherwise physical examination was negative. An intravenous pyelogram showed 2 stones in the pelvic portion of the right ureter. On 20th April 1971 transperitoneal ureterolithotomy was performed. The peritoneal incision over the ureter was not sutured but the abdomen was drained. The following day he was vomiting and the abdomen was moderately distended; bowel sounds were absent. 2 days after the operation he was an ill man with signs of general peritonitis and the abdomen was re-explored. During induction of anaesthesia cardiac arrest took place but the heart was re-started. A large volume of purulent fluid was evacuated from the peritoneal cavity and 2 intraperitoneal drains were inserted and the abdomen closed. Proteus and Coliform organisms were cultured from the peritoneal fluid. During the next few days his condition slowly improved but on 4th May a third operation for burst abdomen was carried out. Thereafter he continued to improve until his discharge from hospital on 19th May. A large incisional hernia was the final legacy of his operations.

Following this unhappy experience of transperitoneal ureterolithotomy our technique was altered. The peritoneal incision over the ureter was securely closed, a stab incision was made in the flank and a tunnel developed from it to the site of the ureterotomy. An extraperitoneal drain was inserted along the track so formed to allow urine to escape without contamination of the peritoneal cavity. In some cases an intraperitoneal drain was also inserted. Results of operations in the next 20 cases in which this technique was employed were entirely satisfactory and no serious postoperative complications were encountered. Our experience was in harmony with that of Michalowski and Modelski (1958) who carried out the same procedure in 3 cases.

Discussion

We do not support Qvist *et al.* in their advocacy of the transperitoneal approach for the removal of stones lying in the abdominal ureter. Our experience confirms that the extraperitoneal approach is very satisfactory and we see no advantage in opening the peritoneal cavity in the majority of cases. There may be special circumstances in which the approach may be considered—for example when multiple bilateral ureteric calculi are present—but so far we have not encountered such indications. On the other hand, these authors are entirely correct in drawing attention to the many advantages of the transperitoneal approach to the lower ureter. The ureter lies immediately under the peritoneum and can be easily identified even in an obese patient. The surgeon is spared the blind dissection of the cellular tissues of the pelvis, which may produce troublesome venous bleeding and which may be especially difficult if there have been previous operations or inflammatory trouble. The transperitoneal approach is quicker and much less traumatic. It is quite clear, however, that leakage of infected urine into the peritoneal cavity is to be avoided at all costs and that satisfactory extraperitoneal drainage must be established before the operation is completed.

Operations on the last 3 to 4 c of the ureter have their own difficulties. In this area the ureter is no longer related to the peritoneum and is crossed by the vas in the male and the uterine vessels in the female. If the ureter is isolated at a higher level it can then be mobilised, drawn upwards above these structures and, whilst supported on the pad of the index finger, may be incised over the stone, which is then extracted. This is usually fairly easy in the female, but in an obese male with a narrow pelvis it may present formidable difficulties. We now usually employ the transvesical approach as described by Barnhouse *et al.* (1973) and Landes, Gavigan and Fehrenbaker (1973) for this type of case.

Summary

The transperitoneal approach to the pelvic ureter has many advantages over the extraperitoneal technique for ureterolithotomy but the operation is safe only if contamination of the peritoneal cavity is avoided by establishing extraperitoneal drainage after closing the incision in the peritoneum over the ureter.

We are grateful to Mr J. R. Geddes for permission to study patients admitted under his care and to Miss Y. White for secretarial assistance.

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Urological Complications following Aortofemoral Bypass Graft

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Urological complications caused by pathological states of the great blood vessels in the pelvis are well known. Aneurysm of the aorta (Chapvis, 1968) and Norback *et al.* (1973) or common iliac artery Vollmar (1967) may result in hydronephrosis due to ureteric compression or to fibrotic reaction round the aneurysm. Congenital anomalies like retrocaval ureter (Considine, 1966) or retro-iliac ureter (Corbus, Estrem and Hunt, 1960; Cockett and Fitzgerald, 1963) can also cause hydronephrosis. Retroperitoneal fibrosis may cause unilateral or bilateral ureteric obstruction. Langeron *et al.* (1969) described a case where aorta and inferior vena cava were compressed by retroperitoneal fibrosis.

Nevertheless, only a few reports are available in the literature concerning the urological complications following vascular bypass operations for occlusive diseases of the aorto-iliac bifurcation (Petrone, Dudzinski and Maniatis, 1974). It is a condition which is probably more frequent than suspected. Because its aetiology and treatment are still under discussion we present 3 new cases.

Case Reports

Case 1. A. S., a 51-year-old man, was admitted to the University Hospital because of intermittent claudication in the right leg. Aortography revealed obstruction of aorta and right common iliac artery. On 4th April, 1967 a dacron aortofemoral bypass graft was inserted. Convalescence was uneventful and when discharged the patient was free of symptoms. 9 months after this operation on 1st January 1968 the patient was readmitted because of the sudden onset of the nephrotic syndrome. Blood and urine data confirmed this diagnosis. On excretory urography we were surprised to see a bilateral hydronephrosis. Both ureters were dilated to the level of the pelvic brim, as in retroperitoneal fibrosis (Fig. 1a). Histological examination of a needle biopsy of the kidney showed "membranous glomerulonephritis" and therapy with corticoids and cytotoxic drugs was started. After 3 months there was remission with disappearance of clinical symptoms. On excretory urography we noted a return to normal of the left and a slight improvement of the right kidney (Fig 1b). No operation was performed partly because of the dubious prognosis due to the nephrotic syndrome and partly because the patient refused such intervention. Excretory urography at 6-monthly intervals showed no change.

Case 2. D. M., a 57-year-old man, has a history of bilateral claudication since 1970. Aortography revealed severe stenosis of the infrarenal aorta. On 4th April 1972 a dacron knitted bypass was inserted between aorta and both external iliac arteries. Recovery was uneventful. 6 months later the patient had to be readmitted because of hypertension. Blood and urine investigations were normal. Excretory urography, scanning and Hippuran-nephrography revealed a non-functioning right kidney. This patient who was known to have severe arteriosclerosis was thought to have stenosis of the right renal artery, Aortography showed a normal right renal artery, but all the renal vessels were displaced by hydronephrosis (Fig. 2). The right kidney and ureter were explored in November 1972. We found gross dilatation of the right kidney and ureter to the level of the bypass graft. Because of scarring round the ureter and graft no reconstructive surgery was possible and nephrectomy was performed.

Case 3. C. A., a 58-year-old man, had a history of bilateral intermittent claudication. Aortography revealed stenosis of the aorta at the level of the bifurcation. On 12th March 1971 an aortofemoral bypass graft was inserted. The patient became symptom-free after operation. 18 months later he was readmitted because of vague abdominal discomfort. Excretory urography showed marked hydronephrosis of the right kidney and severe dilatation of the left kidney and ureter to the level of the vascular graft (Fig. 3a). Aortography, prior to insertion of the graft, had shown normal kidneys showing that the ureteric dilatation had developed after the insertion of the graft. Blood

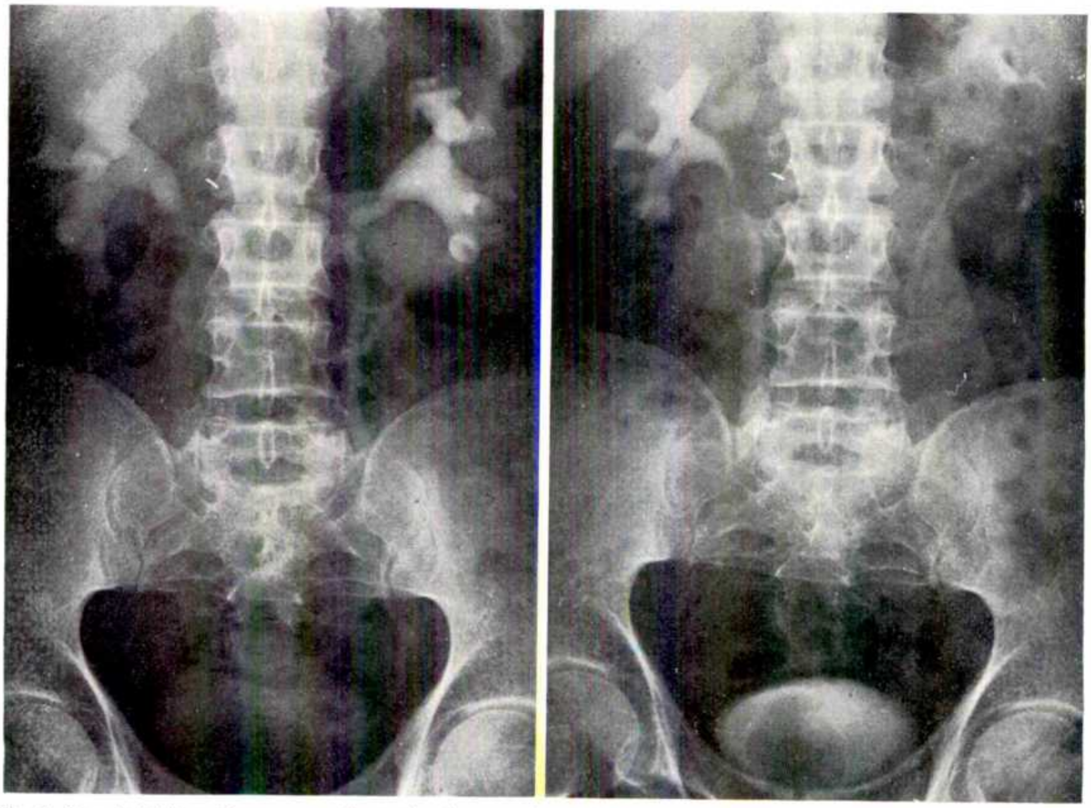

Fig. 1. Case 1; (a) Excretion urogram 9 months after aortofemoral bypass graft; (b) 3 months later, after treatment for membranous glomerulonephritis.

chemistry revealed moderate renal insufficiency. A diagnosis was made of retroperitoneal fibrosis following vascular reconstruction. The patient was given corticoids for 6 weeks which led to slight improvement in the excretory urogram (Fig. 3b). Operation was performed on 3rd August 1973. Gross hydronephrosis and ureteric dilatation were found above the level of the vascular graft. The ureters crossed the vascular prosthesis anteriorly. During dissection which was very difficult because of severe fibrosis, both ureters were opened accidentally and ureteral splints were used. Both limbs of the graft were divided and the ureters were placed posterior to the graft which was re-anastomosed. The ureters were wrapped in sleeves of omentum. During the postoperative period a laparotomy was necessary for intestinal obstruction due to adhesions. A lymphocoele of the right groin was treated conservatively. 6 months later the blood chemistry was normal and excretory urography showed a moderate dilatation of the left ureter and a slight improvement of the left ureter and a slight improvement of the hydronephrosis of the right kidney (Fig. 3c).

Discussion

Ureteric obstruction following aorto-iliac or aortofemoral bypass graft is exceptional; there are only a few reports of this problem in the literature. The first mention was made by Lytton in 1966. He described 2 patients with progressive hydronephrosis after insertion of an aorto-iliacal dacron prosthesis. In both cases the graft crossed the ureter anteriorly and secondary retroperitoneal fibrosis was present. Ureteric obstruction following aortic surgery has been described by Dorfman and Thomford (1968), Ehrlich *et al.* (1972) and Petrone *et al.* (1974). 3 possible aetiological factors were suggested to account for the development of hydronephrosis after aorto-iliac or aortofemoral bypass grafting. These are retroperitoneal fibrosis, pulsation of the graft, and the position of the ureter in relation to the prosthesis.

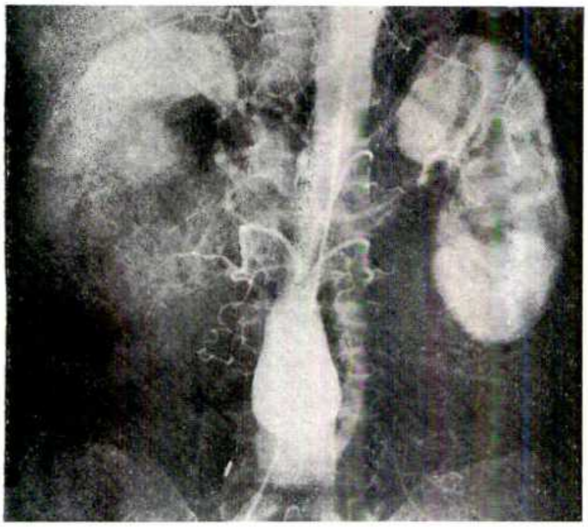

Fig. 2. Case 2. Postoperative aortogram showing right renal vessels displaced by hydronephrosis.

Secondary retroperitoneal fibrosis is always present after reconstructive vascular surgery (Chapvis, Petrone *et al.* and Vollmar). The degree of fibrosis is dependent on factors such as residual haematoma (Chapvis and Ehrlich *et al.*) and the severity of the surgical trauma. Retroperitoneal fibrosis may be the sole factor causing ureteric obstruction as in our first case where the administration of steroids led to nearly complete regression on the left side. It is possible that the continually pulsating graft produces a degree of intramural fibrosis, resulting in a partly mechanical and a partly functional obstruction (Lytton, 1966).

Finally in all the cases with ureteric obstruction reported in the literature, the prosthesis had been placed anterior to the ureter (Dorfman and Thomford, Ehrlich *et al.*, Lytton and Petrone *et al.*). The iliac limbs of an aortofemoral bypass graft are usually inserted after tunnelling digitally between the iliac vessels posteriorly and the peritoneum with the adherent ureters anteriorly. Our third case proves that even when the vascular surgeon preserves the normal anatomical relationship and inserts the prosthesis behind the ureter, ureteric obstruction can occur. The fact that since 1968 we have this complication 3 times, suggests that its frequency is underestimated. Undoubtedly, several cases remain undiagnosed with minor degrees of hydronephrosis and hydroureter if no secondary infection occurs. Unilateral lesions may remain silent even with complete destruction of the kidney as in our second case. Nearly all cases mentioned previously were diagnosed late. This complication must therefore be borne in mind and excretory urography should be performed pre- and postoperatively. (Petrone *et al.*). For treatment of minor degrees of hydronephrosis steroids can be helpful as in retroperitoneal fibrosis (Ross and Goldsmith, 1971). Surgery is necessary when obstruction is severe (Dorfmann and Thomford, Ehrlich *et al.*, Hewitt (1969), Lytton, and Petrone *et al.*). However, if the ureter lies behind the prosthesis, there is still argument about the better method of treatment—division and re-anastomosis of the graft or of the ureter. Lytton, Ehrlich and Petrone performed transection of the ureter and reanastomosis in front of the graft after proximal urinary diversion with a T-tube. This technique had the disadvantage that the graft may be affected by urine extravasation. Hydronephrotic kidneys are often infected and there is a danger of graft sepsis due to extravasation of urine and risk to the life of the patient. We are convinced that an end-to-end re-anastomosis of the ureter always leads to some extravasation of urine even when there is a proximal urinary diversion (nephrostomy, pyelostomy, T-tube, ureterostomy) or insertion of a ureteric catheter. Moreover, healing of the re-anastomosis will be difficult because of poor vascularity due to extensive ureterolysis and general

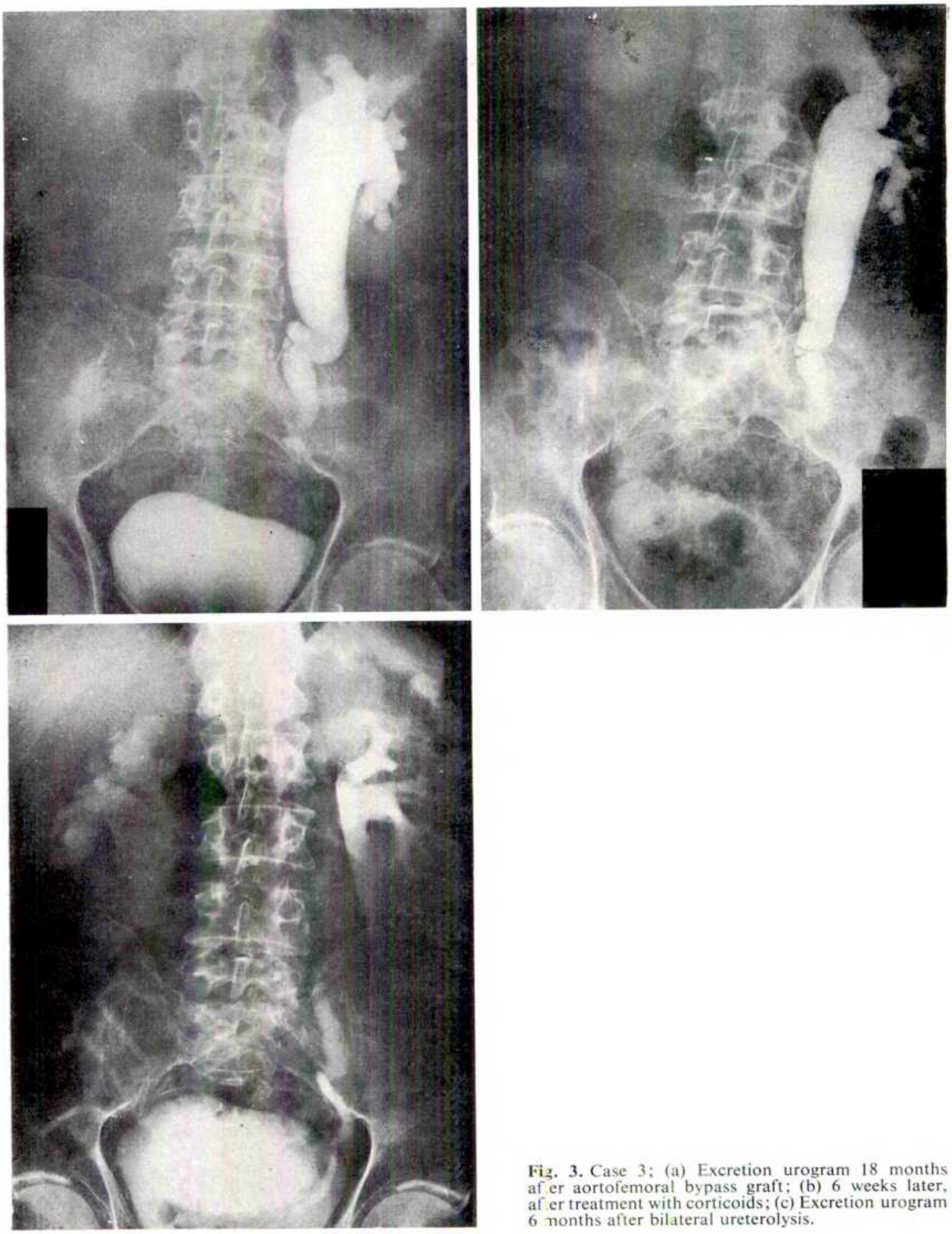

Fig. 3. Case 3; (a) Excretion urogram 18 months after aortofemoral bypass graft; (b) 6 weeks later, after treatment with corticoids; (c) Excretion urogram 6 months after bilateral ureterolysis.

arteriosclerosis. Finally, when re-anastomosis of the ureter is performed, external drainage is needed for at least 10 days which certainly creates the possibility of graft sepsis.

For these reasons we prefer not to open the potentially infected urinary tract but to divide and re-anastomose the graft with transposition in front of or behind the ureter.

Summary

3 cases of ureteric obstruction secondary to aortic femoral bypass grafting are presented.

This complication has been infrequently reported and we feel that it may be more common than is recognised.

In all other published cases the ureter lay behind the prosthesis but the authors present a surgically proved case where the ureter lay in its normal position.

The aseptic vascular reconstructive surgical procedures are to be preferred to ureteric reconstruction.

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Short Case Report

Triplication of Ureter on One Side and Duplication on the Other

A black male, aged 43 years, was admitted with a history of haematuria for 1 year, dysuria and frequency of micturition for 1 week and intermittent episodes of pain in the right iliac fossa. The patient was well-nourished; blood pressure 110/70. All the systems were normal and there was no palpable intra-abdominal mass. Urine examination and blood chemistry revealed no abnormality.

Excretory urography revealed triple ureters on the left and duplication on the right; the upper moiety and fused segment of the right ureter were dilated. There was a ureterocoele on the right (Fig. 1). Retrograde pyelogram showed the triplication on the left and a distal ureteric calculus on the right (Fig. 2).

Comment

The combination of 3 ureters on 1 side and 2 on the other is extremely rare. Since the first publication by Burt *et al.* (1941) to the best of our knowledge only 1 other has been published, by Peterson and Silbiger (1968).

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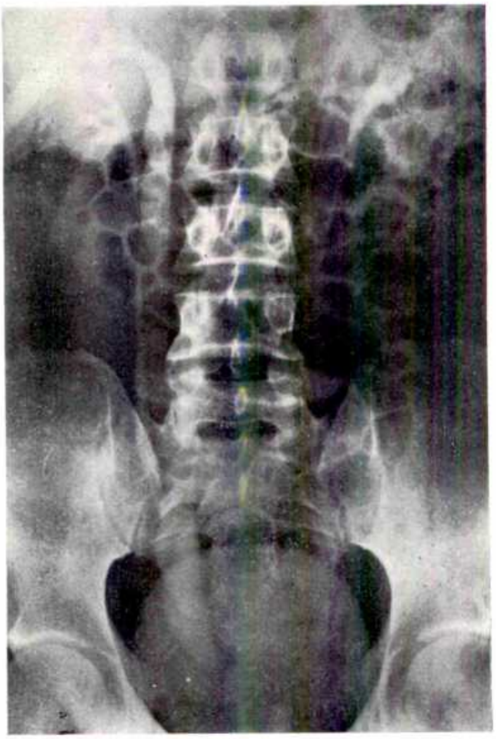

Fig. 1

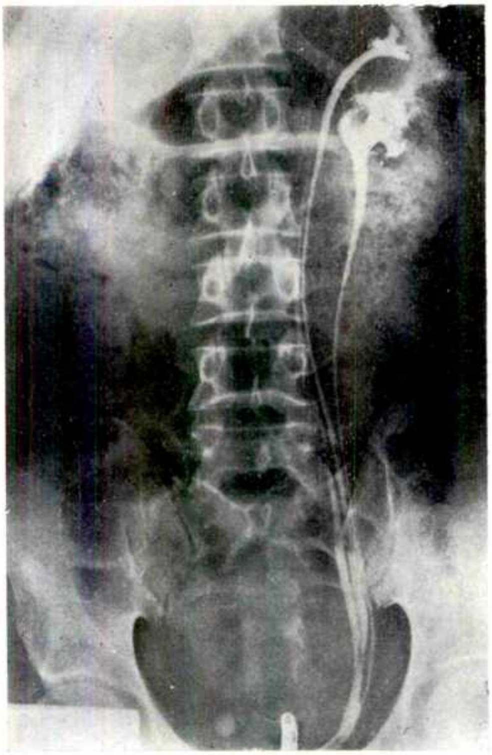

Fig. 2

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Pathogenesis of Ureteric Reflux in Vesical Calculus Disease of Childhood: a Clinical Study

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Ureteric reflux has been widely recognised to cause recurrent urinary tract infection and progressive renal damage. The pioneering experimental studies of Graves and Davidoff (1927), Gruber (1929) Scott (1964) and others stimulated interest in the problem amongst urologists all over the world. The pathogenesis of reflux in infancy and childhood has been investigated in detail by Stephens and Lenaghan 1972; Hutch, 1972; Tanagho *et al.*, 1965; Williams and Eckstein, 1965. Although extensively reported and discussed in the urological literature of the sixties, there is lack of universal agreement on all the aetiologic factors involved in the production of reflux. Significant amongst these is the role of infection which bears a cause and effect relationship to ureteric reflux.

Vesical calculus disease is a problem of considerable magnitude in the paediatric population of several developing countries especially India and Thailand (Anderson, Sriramachari and Khandagale, 1963; Aurora, Taneja and Gupta, 1970; Halstead, 1961; Unakul, 1961). It is believed to be a deficiency disorder on account of its occurrence in children belonging to the poor socio-economic groups (Aurora *et al.*, 1970). In a later urological study of 52 children with vesical calculus disease, about 50% of the patients were found to reveal ureteric reflux (Taneja, Mall and Mittal, 1970). The frequent association of reflux to vesical calculus disease in children had posed two important problems, that is, firstly the factors responsible for reflux and secondly the management of reflux in such cases (Taneja *et al.*, 1970). In order to evolve a rational approach to the problem, a clinico-radiographic study with a long term follow-up of all the children suffering from lower urinary tract calculi was undertaken. The clinical investigation was combined with an experimental study on dogs(Taneja *et al.*, 1973). The present report deals with the clinical aspects of this study.

Patients and Methods

A total of 101 children were treated for lower urinary tract stones at the Urology Unit of Irwin Hospital, New Delhi during the period of 4 years from July 1966 to June 1970. Complete urological investigations as described earlier (Sharma *et al.*, 1973) were performed on 77 infants and children suffering from bladder stone disease. These patients were divided into 2 groups:

Group I: Vesical calculus with reflux—34 patients.
Group II: Vesical calculus without reflux—43 patients.

The ureteric reflux was classified and graded according to the classification proposed by Lattimer *et al.* (1963) and Bridge and Roe (1969). After operation, the children were followed-up through the Clinic at regular intervals. All the children available were submitted to repeated urine culture, excretory pyelography and voiding cysto-urethrography. A critical analysis of the clinical and radiological findings along with management of the 34 children belonging to group I is being presented.

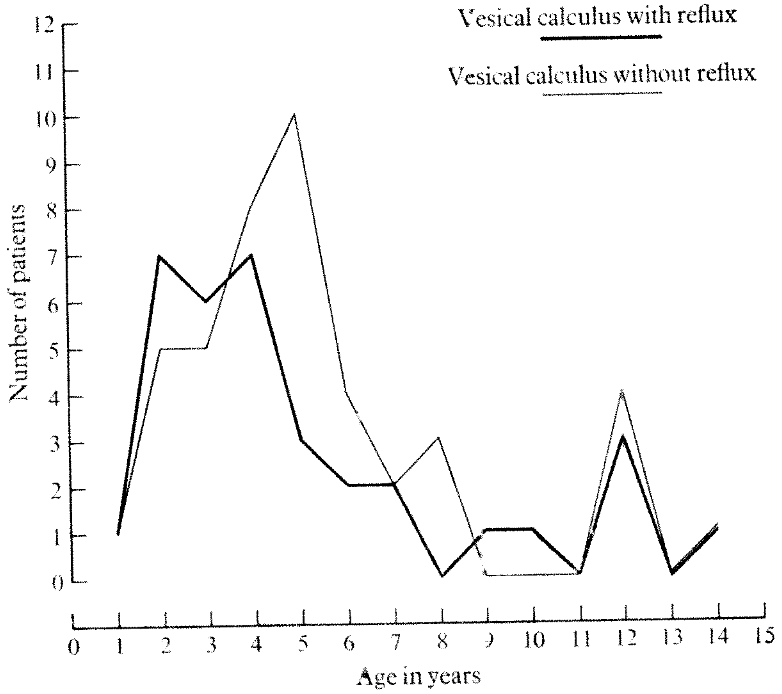

Fig. 1. Age distribution

Observations

Age and Sex (Fig. 1)

21 out of the 34 children, that is, 61·8% in group I were under 5 years of age compared to 19 out of 43 children or 44·2% in group II. The sex distribution was almost similar in the two groups. In group I with reflux, there were 32 males and 2 female children.

Clinical Presentation

The symptoms which brought these patients to the hospital are listed in Table I and compared to the findings in the previous study of 61 cases (Aurora *et al.*, 1970).

Bacteriology of Urine

Urine for culture was available in 33 children preoperatively. The culture was sterile in 13 cases and only contaminants were grown in 4 children. There was significant bacteriuria in 15 patients; single in 13 and mixed infection in 2 patients. The commonest oropathogens isolated in their order of frequency were *Escherichia coli* (6); *Klebsiella* species (4); *Streptococcus fecalis* (2); *Proteus* species (2); *Pseudomonas pyocyanea* (2) and *Staphylococcus pyogenes* (1). The infection rate of 45·4% in this group was higher than the incidence of 36·0% in non-refluxing patients reported earlier (Taneja *et al.*, 1970).

Radiographic Findings

Plain film: a single radio-opaque shadow was seen in the region of the urinary bladder in 31 patients and 3 patients had multiple shadows. This density was laminated in 9 patients and was poorly visualised in another 7 patients. 4 children also had renal calculi and 2 had urethral calculi as well as vesical stones.

Excretory pyelography (Table II): only 26 children could be submitted to preoperative excretory pyelography. Hydronephrosis with hydroureter were the most significant findings on excretory pyelography. In bilateral cases, there were grade IV changes in 2 cases and grades I and II in 1 case each. In unilateral hydronephrosis, the changes were of grade III type in 1 case on either side; grade II in 1 case on the right side; and grade 1 in 2 and 3 patients on the right and left sides respectively.

Table I

Symptoms of Stone

Symptom	Number of Patients	Aarora *et al.* (1970)
Total Patients	34	61
Pain during Micturition	34	44
Frequency of Micturition	26	29
Dribbling and Enuresis	26	22
Intermittent Fever	18	Not recorded
Haematuria	16	19
Suprapubic Pain	15	12
Retention of Urine	5	2
Pyuria	5	Nil
Past History of Stone	2	Nil

Table II

Changes on Excretory Pyelography

Findings	Number of Patients		
	Bilateral	Right	Left
Normal Pyelogram	10	3	4
Non-Functioning Kidney	0	1	0
Delayed Excretion and Damaged	1	0	0
Hydronephrosis and Hydroureter	4	4	3
Ureterectasis	1	1	1
Duplex System	0	1	1
Bifid Pelvis	0	0	1

Voiding Cysto-urethrography

The bladder outline was irregular due to trabeculation and diverticula in 3 cases; filling defects due to mucosal oedema in 2 cases and paraureteral saccules in 1 patient. There was constriction or posterior indentation at the bladder outlet in 11 cystograms with post-stenotic dilatation of the urethra in 10 cases. In 4 cystograms, there was evidence of posterior urethral valves—2 cases, stricture with recto-urethral fistula in 1 case and anterior urethral diverticulum in 1 case. The type and degree of ureteric reflux in these 34 patients (Table III) varied from side to side in bilateral cases.

Endoscopic Findings

Mucosal oedema and inflammatory changes were noticed in 21 out of 29 patients. These changes were maximum at the bladder neck and over the trigone and a circumferential funnel shaped segment of bladder wall starting proximal to the outlet and including the ureteric orifices. The latter were obscured by these changes in many of the cases; but 10 ureteric orifices on the right side and 7 on the left side were wide open and patulous. The vesical outlet appeared narrow in 18 cases.

Aetiological Considerations (Table IV)

On correlation of the radiological, endoscopic and operative findings, the aetiology of ureteric reflux could be attributed to various diseases (Table IV).

Management (Table V)

Primary lesion: excluding the 2 children who left the hospital without treatment, the operative procedures employed to remove the stone and correct the associated uropathy are presented in table V. Ureteroneocystostomy to correct reflux was performed in 9 patients on 11 units. The extravesical tunnelling procedure described by Lich, Howerton and Davis (1961) and Grégoir and van Regemorter (1964) was undertaken for bilateral reflux in 2 cases and left reflux in 1 patient. Reimplantation by Leadbetter-Politano technique was chosen for unilateral reflux on the right

Table III

Incidence and Nature of Reflux

Nature of Reflux	Number of Patients		
	Bilateral	Right	Left
Number of Patients	17	7	10
Degree of Reflux: Grade I	6	2	4
Grade II	10	3	2
Grade III	4	1	1
Grade IV	0	1	3
Type of Reflux: Low Pressure Type	13	5	7
High Pressure Type	4	2	3

Table IV

Aetiolog Considerations

Causative Lesions	Number of Patients
Vesical Calculus	16
Suspected Bladder Neck Contracture	10 (8)*
Posterior Urethral Valves	2 (2)*
Phimosis or Urethral Diverticulum	3
Traumatic Stricture and R.U. Fistula	1
Duplex Kidney	2
Associated Ureterocele	1*
Associated Renal Calculus	4
Associated Urethral Calculus	2

* Figures in brackets denote patients in whom Y-V plasty was performed.

side in 2 and left side in 3 ureters. In 1 child, ureteric reimplantation by Paquin's technique was employed and William's advancement operation was done on 1 ureter with recurrent reflux.

Complications

There was obstructive anuria in one child after bilateral tunnelling operation but it was relieved by immediate re-operation. There was wound infection in 2 children and urinary infection in 5 patients. 7 children had temporary urinary fistula and respiratory infection occurred in 2 cases. One child died of septicaemia and renal failure following nephrostomy. Another child was readmitted for recurrent calculus which was spontaneously voided per urethram.

Results (Table VI)

Excluding one hospital death, 24 of these children were periodically followed up to the end of 1972. The duration of follow-up varied from 7 months to 68 months. For evaluation of results these patients were subdivided into two subgroups: (i) conservative in whom stone was removed but antireflux surgery was not done and (ii) surgical—who had antireflux surgery.

Discussion

Ureteric reflux has been broadly classified into "Primary Reflux" when there is no obstructive or neurogenic lesion in the lower urinary tract and "Secondary Reflux" when there are inflammatory, obstructive, iatrogenic, neoplastic or neurogenic lesions interfering with the function of the

Table V

Management

Operative Procedure	Number of Patients	Antireflux Operations
Suprapubic Cystolithotomy	17	3
Y-V Ant. Vesico-urethroplasty	10	4
Circumcision and Cystolithotomy	2	1
Urethral Diverticulectomy and S.P. Cystolithotomy	1	1
Dilation Urethra and Cystolithotomy	1	0
Bilateral Nephrostomy	1	
Removal of Renal Calculi	4	0

Table VI

Results on Follow-up

Result	Conservative Group	Antireflux Surgery Group
Duration of Follow-up (months)	7 to 59	15 to 68
Untraced	8	1
Died in Hospital	1	0
Clinical: Asymptomatic	14	6
Urinary Symptoms	2	2
Urine Culture: Sterile	12/15	5/7
Infected	3/15	2/7
Reflux: No Reflux	13/14	3/5
Present	1/14	2/5

uretero-vesical junction. Amongst the aetiological factors responsible for secondary reflux, vesical calculus is mentioned along with tuberculosis, interstitial cystitis, bilharziasis and new growths etc. Graves and Davidoff (1927) produced reflux in dogs by insertion of concretions into the bladders. Apart from this experimental observation, the association of reflux to vesical calculus has not been reported in any of the clinical series from the western countries as the vesical calculus disease of childhood is not seen in those countries. Kesavan and Ramakrishnan (1971) found vesical calculus in 4 out of 35 children with reflux. The implications of the underlying urological disease in the aetiology of vesical calculus disease of childhood had been discussed earlier (Taneja *et al.*, 1970). Mention was also made of the frequent association of ureteric reflux to vesical calculus disease of children. The problem of ureteric reflux in such patients required a critical reappraisal on long term follow-up.

Vesical calculus disease is not seen in breast-fed children below the age of 1 year. Ureteric reflux appeared to be more common in children below the age of 5 years as compared to non-refluxing children with vesical calculus (Fig. 1). This tendency to reflux in the presence of vesical calculus seemed to diminish with age. Many of these children had presented with symptoms of infection and retention of urine (Table I). This was further confirmed by a higher percentage of infected urine on culture. Ureteric reflux is well known to cause recurrent and persistent urinary tract infection which is eradicated after antireflux operations. Vesical calculus with superadded infection could have precipitated the onset of reflux in a child with marginal competence of the uretero-vesical valves. Once reflux had set in, this itself would have perpetuated the infection.

The aetiological factors responsible for the causation of reflux in these children (Table IV), included 9 children who had either obstructive uropathy or congenital lesions of the uretero-vesical junction system or ureterocele. These lesions by themselves could have caused ureteric reflux without the presence of a vesical calculus. The associated renal calculi were found in the refluxing pelvis with grade III and IV reflux. On examination these renal calculi were similar in composition to the vesical calculi and thus were the result of ascending infection.

During the earlier stages of this work, some of these children were suspected to be suffering from bladder neck contracture on the basis of radiological and endoscopic appearances. This would account for the 10 patients included under the heading of "suspected bladder neck obstruction" (Table IV). On retrospective review of the X-ray films in 1972 none of these 10 patients including 1 case with ureterocele, had a classical picture of bladder neck obstruction. These radiological and endoscopic changes were the result of mucosal oedema and inflammation resulting from stone which disappeared on repeat cystograms after its removal.

The ureteric reflux in 25 patients could therefore be attributed to the vesical calculus with or without infection. The urinary tract changes caused by a stone in the bladder are: (i) inflammatory changes in the bladder; (ii) obstructive changes affecting the upper urinary tract; and (iii) spasm of the detrusor muscle and intermittent obstruction at the vesical outlet leading to raised intravesical pressure. Concomitant infection and calculus aggravated all these changes.

The role of mucosal oedema and bladder inflammation in the pathogenesis of ureteric reflux is well recognised. According to Graves and Davidoff (1925); and the histological studies conducted by us on the ureterovesical junction of the dogs with bladder stones, revealed inflammatory oedema and fibrosis around the intravesical ureter making it a rigid tube which abolishes the valvular action of the ureterovesical junction. These changes along with the raised intravesical pressure due to irritability and hypertonicity of the detrusor precipitated the onset of reflux. The changes in the upper urinary tract were the outcome of reflux, ascending infection and obstruction at the uretero-vesical junction. In 13 out of 14 patients (92·0%) the reflux was eradicated by the simple removal of the stone. This also led to regression of changes in the upper urinary tract and disappearance of infection. These clinical observations were further supported by the findings of an experimental study on dogs (Taneja *et al.*, 1973).

Conclusions

The management of reflux in vesical calculus disease without any obstructive lesion requires simple removal of the stone in the majority of such cases. Antireflux operations are not indicated in grade I and II degree of reflux.

Grades III and IV reflux which often occur in association with some distal obstruction, require antireflux operations. The inflammation, oedema, hypervascularity and hypertonicity of the bladder wall render intravesical operations difficult. Extravesical ureteroneocystostomy by Paquin or Lich and Gregoire technique are more suitable in such cases (Taneja and Sharma, 1974).

All children suffering from lower urinary tract stones should be submitted to a detailed urological study and follow-up, especially those with ureteric reflux.

Summary

A clinical, radiographic and endoscopic study of 34 children suffering from vesical calculus disease and manifesting ureteric reflux has been presented.

The oedema and inflammatory changes from the vesical calculus and infection were responsible for the reflux in the majority of these children. The reflux was eradicated by simple removal of the stone.

The importance of detailed urological investigation of all the children presenting with lower urinary tract calculi has been emphasised.

I am grateful to Dr O. P. Bhardwaj, Professor of Radiology and Dr K. P. Mittal, Lecturer in Radiology for their valuable help in radiographic studies on these children Dr M. P. Mall and Dr K. C. Sharma formerly post-graduate trainees in the unit helped in the clinical study and follow-up of these patients. My special thanks are due to the Director-Principal, Maulana Azad Medical College and Associated Hospitals, New Delhi for kind permission to undertake this study and to publish this work.

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Short Case Report

Haemorrhage from Stomal Varices in an Ileal Conduit

A case of "caput medusae" developing in an ileal conduit is reported.

Case Report

A 72-year-old ex-army officer underwent total cystectomy with urinary diversion into an ileal loop (Wallace "69" Technique) for bladder carcinoma. 2 years later, he was admitted with haemorrhage from the stoma amounting to 500 ml. He gave a history of intermittent minor blood loss for about 3 months. Examination failed to reveal a cause for the bleeding. Intravenous pyelography and a loopogram were normal. The haemorrhage settled spontaneously. He was re-admitted 4 months later with severe bleeding. Dilated veins of the anterior abdominal wall were noted for the first time. Haemoglobin was 4·9 gm%. Following transfusion, the stoma was examined under anaesthetic. At the mucocutaneous junction of the stoma there was a ring of small varicosities up to a maximum of 0·5 cm in diameter (Fig.). The conduit was freed, the terminal part excised and the stoma refashioned. Postoperatively, he developed chest complications and uraemia and died. Postmortem examination confirmed cirrhosis. There was no recurrent carcinoma nor evidence of oesophageal varices.

Comment

Reports in the literature of bleeding from porto-systemic venous anastomotic vessels around ileostomies are few (Bloor and Orr, 1961; Hamlyn *et al.*, 1974). This would appear to be the first reported from an ileal conduit. It is interesting to note the absence of the oesophageal varices (Eade, Williams and Cooke 1969). Although refashioning of a stoma is a relatively minor surgical procedure, with an ileal conduit there may be only a limited length of bowel available for excision.

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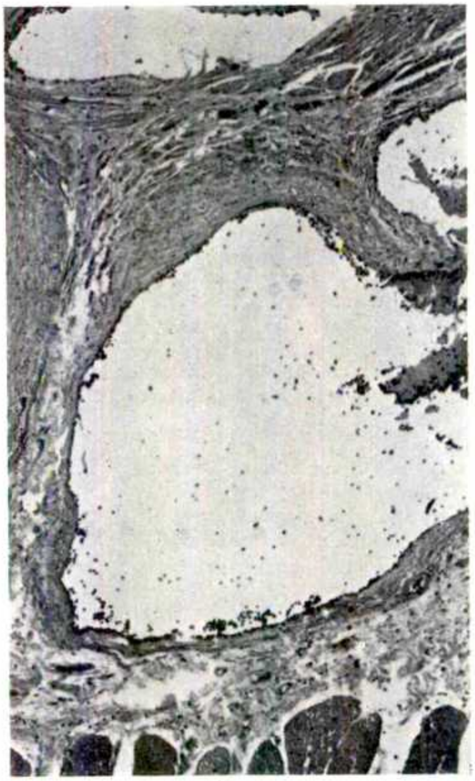

Fig.

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The Management of Pyocystis following Ileal Conduit Urinary Diversion in Children

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Infection in the defunctioned bladder occurs in one-fifth (Eckstein and Mohindra, 1970) to one-third (Smith, 1972) of children following ileal conduit urinary diversion. In the management of this distressing problem the clinician has several modes of therapy available and we report the experience in a large series of children undergoing urinary diversion.

Patients

The records of 113 patients who underwent ileal conduit urinary diversion between 1961 and 1973 were reviewed. All patients had been operated upon by the senior author (H. B. E) or an assistant under his direct supervision. Of this group, 27 (24%) (26 females and 1 male) developed purulent urethral discharge postoperatively. All patients had myelomeningocele with neuropathic bladders and had had urinary diversion for progressive upper urinary tract deterioration (14 patients) incontinence (11 patients), or uncontrolled urinary infection (1 patient). The age at diversion ranged between 6 months and 11 years, and the initial signs and symptoms of pyocystis were evident within 3 months after surgery in all patients. 16 of the patients had been intensively treated or hospitalised for severe urinary infection (*i.e.* pyrexia, loin pain, leucocytosis) prior to diversion.

Techniques and Results

1. All patients were treated initially by repeated bladder irrigation with antiseptic (Hibitane, Noxyflex) or antibiotic (Neomycin, Polymixin) solutions. Treatment usually consisted of washing out the bladder once or twice weekly for a month. 11 patients responded to this regimen, although in most cases the cycle of treatment had to be repeated several times before the infection was finally controlled.

2. 11 patients in whom bladder discharge was persistent or rapidly recurring, in spite of frequent irrigations, underwent cystectomy. Surgery was straightforward and uncomplicated and apart from wound drainage, there was negligible postoperative morbidity.

Since 1973 there have been 5 additional patients who have failed to respond to conservative management. In these patients, vaginal vesicostomy modifying the procedure originally described by Spence and Allen (1971), was performed using the Payr's intestinal clamp. One blade of the clamp was introduced into the vagina and the other into the urethra for a distance of 5 cm and the clamp was then occluded for 5 min. Following this the crushed urethro-vaginal septum was incised until the index finger could be easily inserted into the bladder. No sutures were used. The vaginal and bladder cavities were packed for 48 hours. There have been no intra-operative or postoperative complications. In all cases, bladder discharge ceased or became negligible within several days and has not recurred.

Discussion

Pyocystis is usually manifested by profuse, malodorous "vaginal" or urethral discharge but on occasion can also cause systemic signs of infection. The incidence is much higher in females, presumably because the short urethra predisposes to ascending infection. It tends to occur more frequently in those children who have had recurrent urinary infection, particularly with Proteus species, prior to diversion (Eckstein and Mohindra, 1970).

The response of pyocystis to bladder irrigations is primarily related to how vigorously treatment is carried out. There is reluctance to admit the child to hospital to treat a seemingly trivial infection and, on the other hand, there is difficulty in getting this type of treatment accomplished in the home or clinic. The haphazard treatment that usually results explains, in part, why it is variously reported that 2·8% (Richie, 1974) to 14% (Eckstein and Mohindra, 1970) of patients undergoing diversion will require surgery for troublesome persistent discharge.

An obvious solution to prevent pyocystis is to perform cystectomy at the time of urinary diversion. This has, however, the disadvantage of prolonging a major operation, with attendant increased morbidity and blood loss in children, many of whom are already in serious difficulty with compromised renal function. In addition, as only a minority of children undergoing diversion will develop pyocystis, it seems unwise to perform concomitant cystectomy on every patient. Lastly, cystectomy at the time of diversion makes the operation irreversible in terms of future lower urinary tract reconstruction.

Delayed cystectomy, after failure of medical treatment has long been used in cases of pyocystis. In general the operation presents no difficulty, but it is a major procedure requiring prolonged general anaesthesia. Discharge from hospital is often delayed due to purulent drainage from the pelvic drain and blood transfusion is often required in the young child.

In 1971 Spence and Allen described their experience in the use of vaginal vesicostomy in treating women with pyocystis. It proved difficult to adapt their procedure to the young child because the confined space of the vagina made it difficult to visualise the vaginal septum and suture the edges of the vesicostomy. The Payr's intestinal clamp is ideally suited because its shape conforms to the operative field and its wide crushing blades provide adequate haemostasis without need of suturing. The operation can be easily performed in less than 10 min under light anaesthesia and blood loss is negligible. Once free vesico-vaginal drainage is established, the purulent discharge rapidly resolves without further therapy. Orecklin and Goodwin (1974) have described the use of perineal vesicostomy as an alternative to cystectomy in the male patient with pyocystis but this procedure is as lengthy as cystectomy and requires diligent follow-up to ensure its patency.

Finally the operation of prophylactic vagino-vesicostomy at the time of urinary diversion deserves discussion. Unlike cystectomy (as discussed) vagino-vesicostomy adds little operative time, operative risk or blood loss to a diversion procedure. However, by creating a large fistula between the bladder and the vagina the procedure is rather finite and makes the theoretical restoration to the *status quo* before diversion almost impossible. For this reason we have, to date, not used or advocated prophylactic vagino-vesicostomy and we know of no published series where this combination of operations has been tried. As the incidence of pyocystis following diversion in children is only 24% we feel, for psychological rather than strictly surgical reasons, that prophylactic vagino-vesicostomy is not a justifiable procedure.

Summary

27 cases of pyocystis following ileal conduit urinary diversion are discussed.

In those cases not responding to medical treatment, vagino-vesicostomy is recommended as an alternative to cystectomy.

The operation of prophylactic vagino-vesicostomy at the time of the original diversion is discussed.

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Prolonged Bladder Distension in the Treatment of the Unstable Bladder

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The symptoms of frequency, nocturia, urge incontinence and enuresis are usually associated with demonstrable bladder instability on cystometry, which may be due to urinary infection, outflow obstruction or bladder neuropathy. Eradication of infection and relief of outflow obstruction where applicable can confidently be anticipated to relieve the instability. However, there remains a large group of patients, whose symptoms often date back to childhood, in whom no aetiological factor can be found. Treatment in those with idiopathic instability remains very much less successful.

Treatment with ganglion blocking drugs such as emepronium bromide, or with anti-muscarinic drugs such as propantheline and imipramine (Gregory, Wein and Schoenberg, 1974), or with musculotrophic drugs such as flavoxate hydrochloride (Stanton, 1973) may relieve symptoms and change the pattern of the cystometrogram in a number of patients, but there remains a significant proportion in whom drug therapy is ineffective. Many surgical procedures have been advocated in the past, including selective sacral neurectomy (Torrens and Griffith, 1974), cystocystoplasty (Turner-Warwick and Ashken, 1967; Essenhigh and Yeates, 1973), entercystoplasty (Gibbon, 1967) and multiple detrusor myotomy (Mahony and Laferte, 1972). None of these procedures has proved to be universally successful or long lasting. A recent report (Dunn, Smith and Ardran, 1974) of the effectiveness of prolonged bladder distension prompted us to assess the value of this form of treatment.

Patients and Methods

11 patients underwent 12 bladder distensions. All had undergone thorough urodynamic investigation including a detailed history and examination, urine culture, full blood count, blood chemistry,

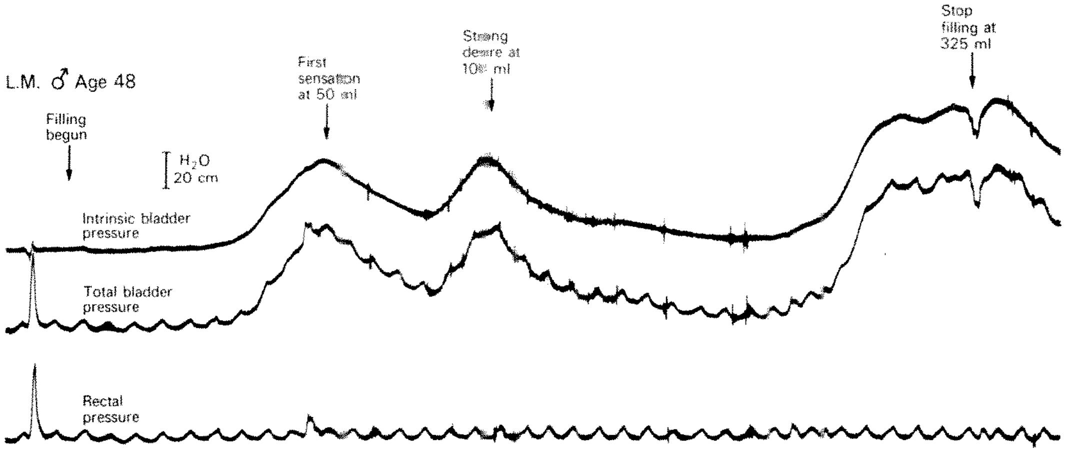

Fig. 1. Cystometrogram showing bladder instability.

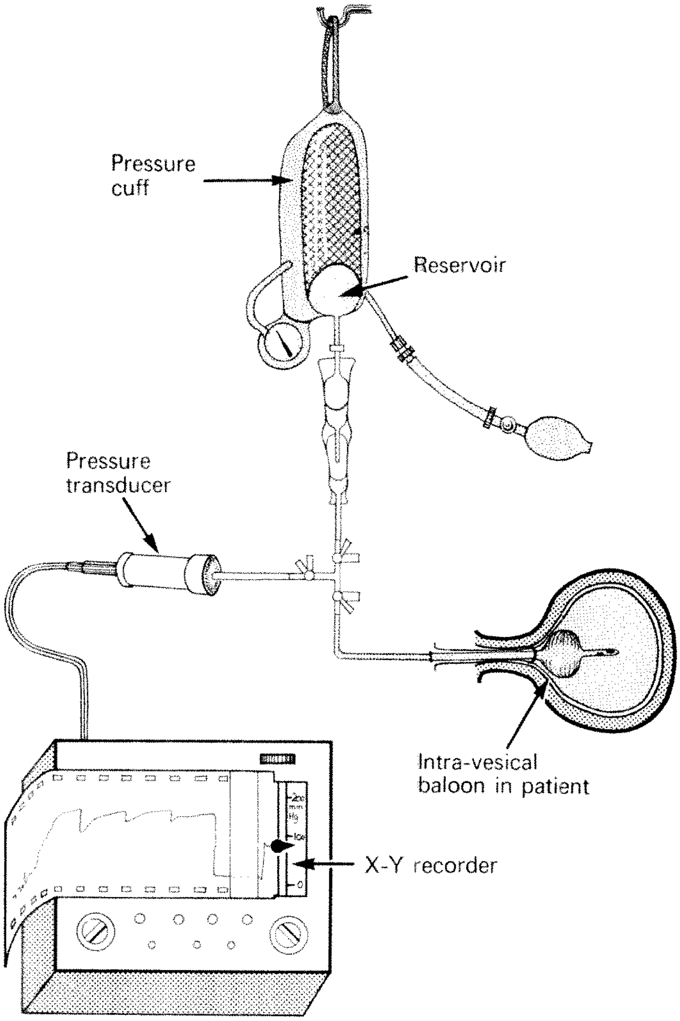

Fig. 2. Diagram of apparatus employed in modified Helmstein bladder distension.

cystometry, intravenous urography and pressure/flow studies combined with cystography. All patients demonstrated unstable systolic detrusor contractions during cystometry (Fig. 1) which was performed at a filling rate of 150 ml per min with the patient seated.

Symptomatology varied from patient to patient but all had some degree of frequency, nocturia and urgency and all had either urge incontinence and/or enuresis.

Before being offered bladder distension all patients in the group had failed to respond to drug therapy and their incontinence was of sufficient severity to be a disability rather than a nuisance. In 9 patients no cause for the bladder instability was demonstrated and they have been labelled as idiopathic instability, while the 2 remaining patients were known to have disseminated sclerosis and the bladder symptoms were their main complaint.

8 of the 12 distensions were performed under epidural anaesthesia, the remainder under general anaesthesia. In 2 patients with disseminated sclerosis general anaesthesia was chosen electively and in 2 patients epidural anaesthesia failed.

Following cystourethroscopy the bladder was distended by an intravesical balloon after the

Table I

Symptomatology before and after distension

	Symptoms before distension					Symptoms 1 month after distension				
Patient	Urgency	Frequency	Nocturia	Urge incontinence	Enuresis	Urgency	Frequency	Nocturia	Urge incontinence	Enuresis
RT F 39	+++	1 hrly	Wet	+++	+++			No change		
JD F 48	++	1 hrly	2	++	–	+	1 hrly	2	+	–
EP F 52	+++	½ hrly	4	+++	+++			No change		
MI F 43	+++	½ hrly	3	+++	++	++	1 hrly	2	++	–
BL F 37	+++	½-2 hrly	3	+++	+			No change		
EOM F 26	+++	1 hrly	2	++	++	++	1-2 hrly	1-2	++	–
EP F 52	+++	½ hrly	4	+++	+++			No change		
AH F 28	+++	½-1 hrly	2	+++	–			No change		
JM M 34	+++	1 hrly	2	++	–	++	1-2 hrly	2	++	–
LM M 48	++	1½ hrly	Wet	+	+++	+	2 hrly	Wet	+	+++
VB F 54	+++	10 min 2 hrly	6	+++	+			No change		
IB F 47	+++	1-2 hrly	3	++	++	++	1-2 hrly	0	+	–

– = Nil, + = Mild, ++ = Moderate, +++ = Severe.

method described by Helmstein (1972). Via a 3-way tap the intravesical balloon was connected to a 1 litre reservoir of Hartmann's Solution which was pressurised with a Fenwal pressure infusor. The third limb from the 3-way tap was connected to a pressure transducer and the recorded pressure was displayed on an X-Y recorder (Fig. 2). Intra-balloon pressure was maintained at systolic blood pressure.

The first 3 patients to undergo bladder distension had their bladders distended for 1 hour, 5 patients had their bladders distended for 2 hours and the remaining 4 patients underwent 4 consecutive ½-hour periods of distension. In all patients an indwelling urethral catheter was left *in situ* overnight. Repeat cystometry was performed 48 hours after distension, at 1 month after distension and in 9 patients again at 4 months after distension.

Results

6 patients noted some improvement symptomatically which was assessed as marginal by 4 and moderate by 2 (Table I). In none of these patients did the cystometrogram change from an unstable to a stable pattern though on cystometry the capacity increased in 3 (Table II). In 2 patients whose symptoms remained unchanged the bladder capacity during the cystometrogram performed in the early postoperative phase had increased, though these 2 patients were unable to void satisfactorily and were left with residual urine volumes of three-quarters of their total capacity so that their functional bladder capacity was unchanged. However, these same 2 patients

Table II

Bladder capacity on cystometry before and after distension

Patient		Diagnosis	Volume(s) at distension Length of distension	Capacity on cystometry before distension	Capacity on cystometry 2 days after distension	Capacity on cystometry 1 month after distension	Capacity on cystometry 4 months after distension
RT 39	F	Idiopathic instability	820 ml 1 hr	100 ml	120 ml	120 ml	Diverted
JD 48	F	Idiopathic instability	1200 ml 1 hr	600 ml	500 ml	600 ml	600 ml
EP 52	F	Idiopathic instability	700 ml 1 hr	50 ml	80 ml	45 ml	60 ml
MI 43	F	Idiopathic instability	1400 ml 2 hr	50 ml	200 ml	400 ml	300 ml
BL 37	F	Disseminated sclerosis	1700 ml 2 hr	100 ml	500 ml	50 ml	150 ml
EOM 26	F	Idiopathic instability	1600 ml 2 hr	500 ml	450 ml	400 ml	350 ml
EP 52	F	Idiopathic instability	800 ml 2 hr	60 ml	45 ml	125 ml	Diverted
AH 28	F	Disseminated sclerosis	1000 ml 2 hr	175 ml	*200 ml	50 ml	..
JM 34	M	Idiopathic instability	800, 1000, 1050, 1000 ml 4 × ½ hr	150 ml	150 ml	75 ml	<50 ml
LM 48	M	Idiopathic instability	600, 850, 900, 1000 ml 4 × ½ hr	200 ml	200 ml	325 ml	..
VB 54	F	Idiopathic instability	550, 600, 600, 700 ml 4 × ½ hr	150 ml	400 ml	250 ml	250 ml
IB 47	F	Idiopathic instability	550, 600, 600, 600 ml 4 × ½ hr	120 ml	150 ml	300 ml	..

* 2 weeks post-distension.

had reverted to their pre-distension cystometry pattern at 1 month. 1 patient who was undergoing distension for a 2 hour period under general anaesthesia was noted to become hypotensive at the end of the procedure. The intravesical balloon was found to have burst and cystoscopy revealed a 5 cm tear in the postero-lateral bladder wall. At laparotomy when the tear was repaired moderate extraperitoneal extravasation of fluid was found to have occurred.

Among the 6 patients who gained some symptomatic relief 1 had a distension for 1 hour, 2 had a distension for 2 hours and 2 had a distension for 4 consecutive ½-hour periods. The length of follow-up in this group varies from 3 to 9 months.

Discussion

Bladder instability which is the cause of disabling symptoms remains a very difficult condition to treat. Drug therapy may moderately improve those whose symptoms are not severe (Stanton 1973), but in general the results of drug therapy are disappointing and often short-lived. It has been suggested (Dunn *et al.*, 1974) that prolonged bladder distension is an effective procedure in the remainder, though the mechanism by which this occurs is unclear.

Mayo *et al.* (1973) have shown that prolonged bladder distension may result in the deposition of intercellular collagen. However, no voiding disorders have been reported following prolonged bladder distension for carcinoma of the bladder, though the intravesical pressures involved may differ in the 2 groups. Theoretically, prolonged bladder distension may result in irreversible ischaemic damage to afferent or efferent nerves, intramural ganglia or to muscle and elastic fibres in the bladder wall, any or all of which changes might result in the diminution of unstable activity on cystometry.

However, in this series prolonged bladder distension was not effective in abolishing unstable bladder contractions. Worthwhile symptomatic improvement occurred in only 2 patients; in both these patients an increased bladder capacity was demonstrated on cystometry.

Summary

11 patients underwent 12 prolonged bladder distensions for bladder instability.

In no case did the cystometrogram revert from an unstable to a stable pattern, though 6 patients noted symptomatic improvement which was attested as moderate by 2 and marginal by 4.

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Automatic Bladder Irrigation after Vaginal Surgery

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After gynaecological surgery, many patients have indwelling urinary catheters to prevent urinary retention. This practice is associated with an increased risk of infection in about a third of patients (Cattell *et al.*, 1963; Chamberlain, Dulake and Kidd, 1968). Various antibiotic and chemotherapeutic regimens are not very effective in preventing or treating this. An investigation was performed, therefore, to see if infection rates might be reduced by rhythmically irrigating and completely emptying the bladder on a tidal flow principle. It was hoped that bladder tone would be maintained, and that residual urine volumes would be reduced.

Method

A survey was conducted on patients having vaginal repair operations. 2 surgical teams were involved but operating techniques were virtually identical; all patients had an indwelling 16 Foley catheter inserted at the end of the operation which stayed for 5 days. From August 1971 to July 1973 all patients who had vaginal repairs, with or without vaginal hysterectomy, were included with the exception of those who had undergone previous vaginal surgery.

Allocation into 1 of 3 groups was made in a random fashion using the last digit of the hospital number. 1 group of patients had continuous gravity drainage into a sterile disposable bag; the second group were irrigated with the Cystomat drainage apparatus using sterile saline as the irrigant; the third group were irrigated with the Cystomat apparatus with irrigation fluid containing polybactrin, neomycin and bacitracin (250 mg of each in 500 ml fluid).

The Cystomat ® is a sterile, disposable device which automatically performs filling and emptying of the bladder with an irrigation solution in a closed system. The principle of the apparatus is an intermittent siphon effect. Towards the end of the irrigating phase, even a slight rise in the intravesical pressure will cause the bladder to be sucked empty before a new cycle begins (Holm and Egeblad, 1970).

It was hoped that this apportioning of patients would differentiate the effects on the urinary tract due to the mechanical aspects of the equipment from the bactericidal effects of bladder irrigation with antibiotics, while providing the conventional gravity drainage group as controls.

Daily urine volumes were recorded and urine samples examined bacteriologically before operation and on the 5th and 10th days. For this survey, a count greater than 100,000 organisms per millilitre was considered indicative of urinary infection. On different grounds, systemic antibiotics were given if clinically indicated by symptoms or signs. On the 5th day, all catheters were removed and if the patient micturated and the bladder was not palpable in the abdomen, no further catheterisation was done. If, however, micturition was difficult or the bladder was palpable, residual urine volumes were removed and measured twice a day until normal function returned.

Results

111 patients participated in the survey. Group 1 was slightly larger (43) than the other two (34 each). The numbers of patients with infected urine are shown in Table I.

Table I

Urinary Infection adjudged by an Infestation of more than 100,000 Organisms per Millilitre

	Group 1			Group 2			Group 3		
	Gravity Drainage n = 43			Cystomat with Saline Irrigant n = 34			Cystomat with Antibiotic Irrigant n = 34		
	Sterile	Infected	Not Known	Sterile	Infected	Not Known	Sterile	Infected	Not Known
Preoperative	31	8	4	29	5	0	22	4	8
Day 5	20	21	2	12	22	0	24	10	0
Day 10	23	13	7	20	12	2	10	24	0

Table II

Re-catheterisations Performed

	Group 1	Group 2	Group 3
	Conventional Drainage n = 43	Cystomat with Saline Irrigant n = 34	Cystomat with Antibiotic Irrigant n = 34
Not re-catheterised	27	24	21
Re-catheterised	16	10	13
Times re-catheterised			
×1	10	5	6
×2	3	2	3
×3	2	3	2
×6	0	0	1
×22	0	0	1
Not known	1	0	0

Systemic antibiotics were given for clinical reasons to 32 (74%) women in Group 1, 31 (90%) in Group 2 and 23 (67%) in Group 3. These are high figures and may have reduced the bacilluria in subsequent urine samples. However, all groups are high and any remaining infection in the urine would be in spite of the antibiotic treatment. Recatheterisation was required for 16 patients in Group 1, 10 in Group 2 and 13 in Group 3.

Table II shows the numbers of patients requiring recatheterisation and the frequency distribution of instrumentation.

Discussion

If rhythmical tidal drainage does improve bladder tone after surgery, it might be expected to reduce the infection rate and number of patients recatheterised compared with conventional gravity drainage. Table I shows the infection rates and although at Day 5 there are suggestive differences between patients in Group 3 and the other women, none of these differences attained statistical significance. By Day 10 however, there is a significant incidence of urinary infection between Groups 2 and 3 ($P<0{\cdot}01$). Because there were patients in Group 1 about whom the urinary bacteriology was unknown, the differences between Groups 2 or 3 and Group 1 are not open to statistical analysis but it is obvious that there is no suggestion of an improvement of either Cystomat group over the gravity drainage patients. Neither is the necessity for recatheterisation for residual urine significantly less frequent after Cystomatic irrigation with, or without, antibiotics in the fluid (37% compared with 34% in the gravity drainage group).

Our thanks are due to Sisters Hyder and Metcalfe and the nursing staff of The Chelsea Hospital for Women who patiently cared for the patients who took part in the survey. We would like to thank Leo Laboratories for the provision of the disposable Cystomats and particularly, Mr J. W. Kyle for his assistance. Antibiotics for the irrigation fluid were kindly donated by Calmic Limited.

Summary

Comparing Cystomatic irrigation of the bladder with conventional gravity drainage, there was no decrease in immediate urinary infection rates nor was there any obvious improvement in the speed of recovery of bladder function.

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Short Case Report

Carcinoma of the Bladder Metastatic to the Tongue

A 62-year-old woman, with a deeply infiltrating, grade IV epidermoid carcinoma of the bladder, was examined extensively for metastatic disease. Results of all studies, including a chest roentgenogram, radioisotope liver scan and bone scan, were negative. Anterior pelvic exenteration was cancelled when biopsy of an isolated tender tongue nodule revealed metastatic epidermoid carcinoma (Fig.). Despite chemotherapy with cyclophosphamide and 5-fluorouracil the patient died with carcinomatosis 5 months after onset of symptoms.

Comment

Carcinoma of the bladder metastasises most commonly to regional nodes, bone, lung and liver. Metastases to the head and neck are unusual, the most common sites being the brain, supraclavicular nodes, neck nodes and skull (Flocks and Boarman, 1973). Dissemination to the thyroid (Fridell and McAuley, 1968) and skin (Hollander and Grots, 1968) has also been reported. To our knowledge no incidence of spread to the oropharynx has been reported. This case is noteworthy because of the unique site of dissemination and the rapid progression from what was believed to be a surgically curable disease to death from carcinomatosis.

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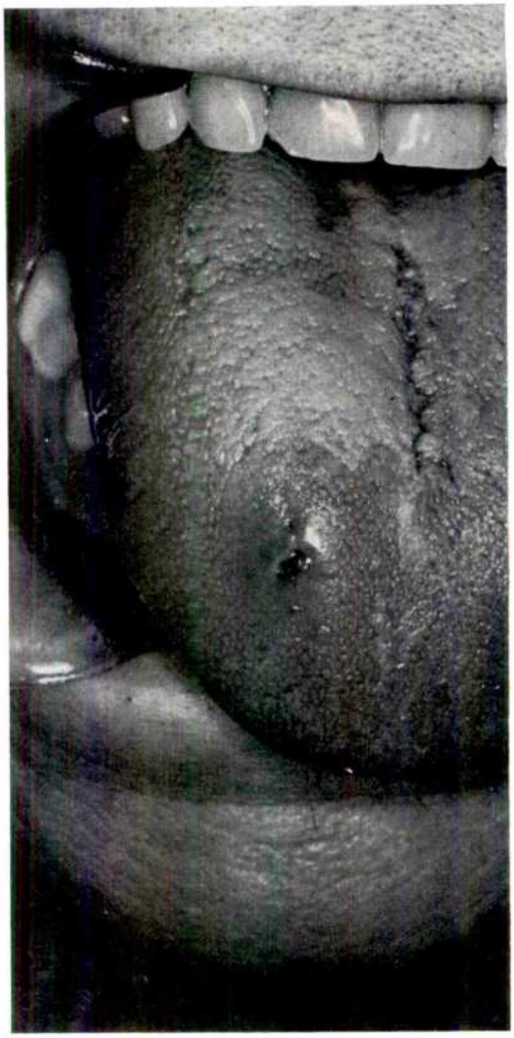

Fig. Slightly raised nodule located near the tip on the right side of the tongue. Small eschar resulted from biopsy.

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Double Bladder with Complete Sagittal Septum: Diagnosis and Treatment

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Duplications are one of the more rare forms of congenital malformations of the bladder.

Case Report

The patient was a 6-year old boy who had been submitted when only a few months old to a series of dilatations for congenital stenosis of the anus. An examination at 12 months of age, following an attack of acute enteritis with high temperature, was recorded as showing a large hypogastric mass and pyuria. The parents refused to allow further investigation as advised since the general condition of the child had improved. Following this episode the mother noticed not only that the child had difficulty in micturition but that this was sometimes painful and the urine often contained a suspension of whitish flakes. The child was first seen by us a month after an attack of severe widespread abdominal pain and dysuria.

Physical examination showed marked abdominal swelling due to a spherical mass about the size of a foetal head occupying the entire hypogastrium. The mass was smooth, tense, elastic, fairly well defined and was not painful. Examination of the external genitalia revealed a right testis palpable in the inguinal canal whereas the left was undetectable. Rectal examination revealed marked hypotonia of the sphincter (the child is also affected by partial faecal incontinence), and a tense elastic mass anterior to the rectum.

Marked pyuria and microscopic haematuria were found. Urine culture gave a growth of *Pseudomonas aeruginosa*.

Intravenous urography (Fig. 1) showed a silent kidney on the left side; the right kidney looked normal. The ureter showed only slight dilatation.

The bladder was situated on the right side of the pelvis; it had a crescentic shape with a well-defined regular outline concave upwards and to the left as if compressed from outside. The post-evacuation film showed a considerable amount of residual urine.

Retrograde cystography confirmed the distortion of the bladder and demonstrated on distension the presence of right ureteric reflux (Fig. 2). It was not possible to perform a cysto-urethrogram due to lack of co-operation of the patient.

A barium enema revealed marked dilatation of the ampulla of the rectum and displacement of the descending and sigmoid colon to the opposite side (Fig. 3).

Cystoscopy showed a deformity of the bladder neck, both from above downwards and from side to side; the vesical cavity was tubular and displaced towards the right; the dome of the bladder was not visible; the left wall was markedly convex. The mucosa looked normal; the ureteric orifices were not seen.

Since the investigation had not established the nature of the abdominal mass, the abdomen was explored.

At operation the findings appeared to indicate a double bladder with complete sagittal septum (Fig. 4). In view of the absence of left renal function a nephro-ureterectomy was performed together with complete resection of the excluded bladder, removing also the entire sagittal septum. Due to the medial position of the right ureter and of its orifice, reimplantation was necessary: the procedure described by Paquin was employed. A sufficiently large reservoir was constructed by approximating the anterior and posterior margins with interrupted sutures.

Intravenous urography 3 years after operation (Fig. 5), showed that the bladder was only slightly asymmetrical and looked almost normal. Retrograde cystography showed no vesico-ureteral reflux.

Discussion

Abrahamson, in 1961, using the classification proposed by Burns, Cummins and Hyman, (1947) (Fig. 6), published a review on the various forms of double bladder referring in each case to reports in the literature. According to this review, 6 cases of complete sagittal septum had been reported since 1838 (Juetting, 1838; Testa, 1896; Boulgakow, 1926; Boulgakow and Malek, 1940;

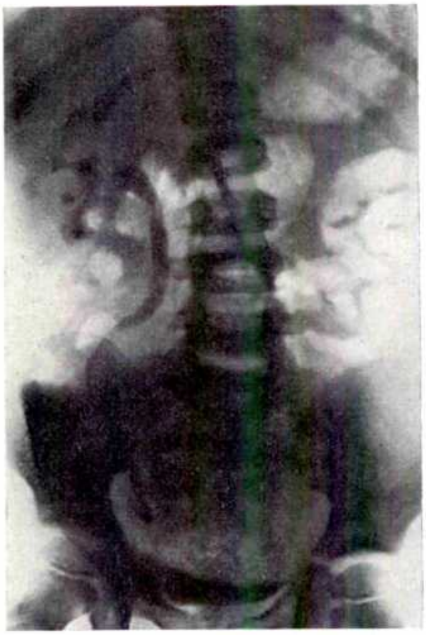

Fig. 1. Urography showing a left silent kidney. The bladder is sickle-shaped as if compressed *ab extrinsico.*

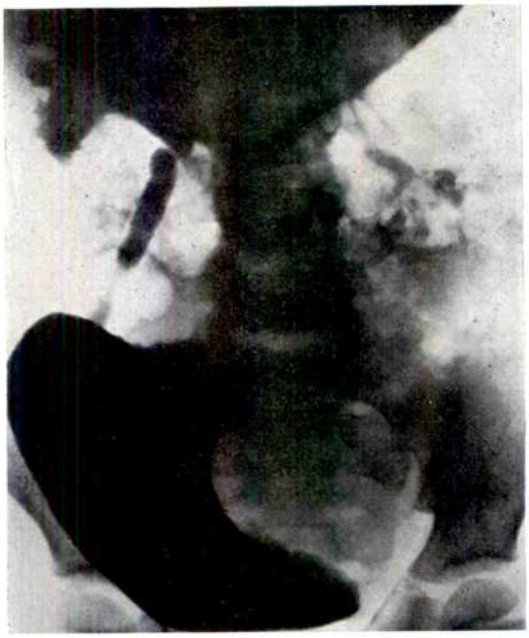

Fig. 2. Retrograde cystography confirming the morphological modification of the bladder. Right vesico ureteral reflux appears.

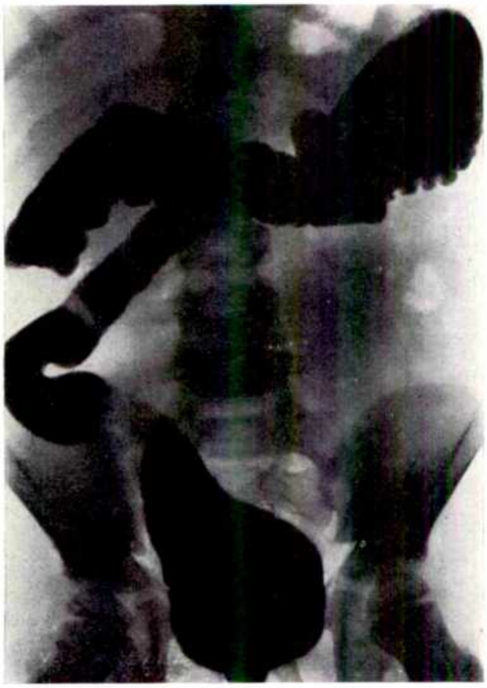

Fig. 3. Contrast enema revealing dilatation of the ampulla recti and displacing the descending colon and sigma.

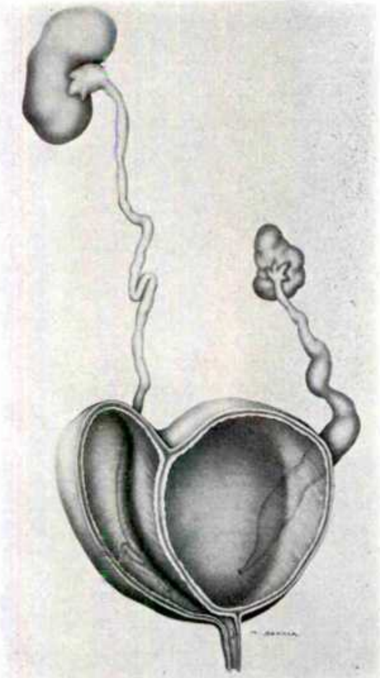

Fig. 4. Situation at surgery: double bladder with complete sagittal septum. Left megaloureter with hypoplastic kidney.

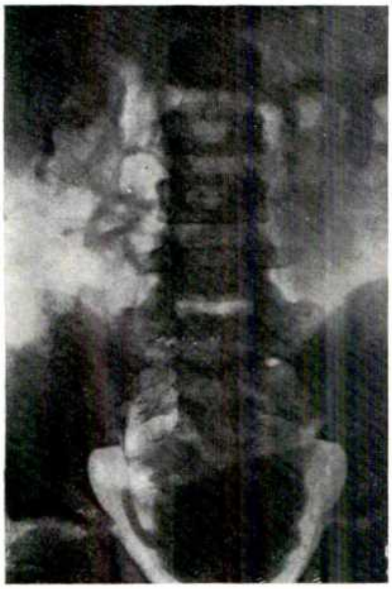

Fig. 5. 3 years follow-up urography.

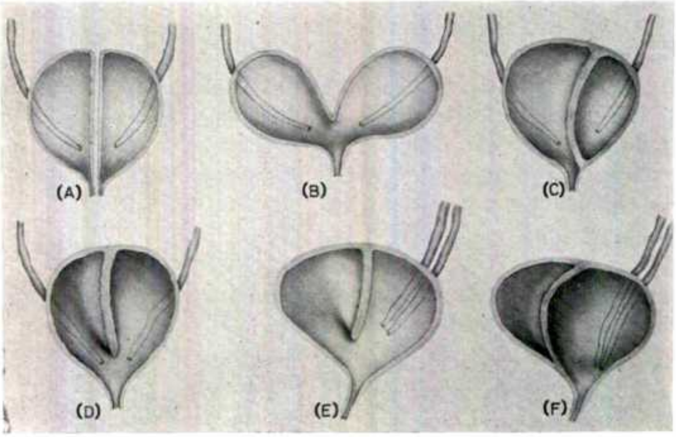

Fig. 6. (a), Complete reduplication. (b), Incomplete reduplication. (c), Complete sagittal septum. (d), Incomplete sagittal septum. (e), Incomplete frontal septum (lateral view). (f), Complete frontal septum (lateral view).

Léon Diaz, 1953; Abrahamson, 1961); however, the author suggests that the case reported by Boulgakow and Malek may in fact have been an ectopic ureterocele. In our opinion the case reported by Léon Diaz should also be excluded since it is most probably a case of complete reduplication of the bladder with double urethra. No further cases have been reported in recent years.

As far as the cases of bladders with complete frontal septum are concerned, although Abrahamson refers to 3 cases, he expresses some doubt as to their authenticity and suggests that these may in fact have been ectopic ureteroceles. Recently, however, Witzleben (1965) and Levallois and Fontaine (1971), described 2 cases which in our opinion appear to be true examples of complete frontal septa.

In spite of numerous attempts no satisfactory explanation for the embryonic origin of these malformations has yet been found.

The hypotheses advanced are varied, and often, even if they appear to explain a particular type of malformation, do not explain the pathogenesis of others. On the other hand, as Abrahamson points out, it is very difficult to determine the abnormal embryology of a system when the normal has not yet been fully elucidated. Whilst the author does not appear to favour any one particular theory, he is of the opinion that a single pathogenic event is responsible for the various types of malformation and suggests that these are the result of a different degree of development of a common malformative error.

From a clinical point of view there are no specific signs to enable early diagnosis of these malformations to be made. In fact, in general, diagnosis in the cases mentioned in the literature was made during investigations carried out following repeated cystitis, disorders in micturition or during explorative surgery performed to establish the nature of a poorly defined hypogastric mass. Nevertheless, as far as bladders with a sagittal septum or complete frontal septum are concerned, these are characterised by the presence of an abdominal mass which is usually very large and presents the characteristics of a cystic swelling which does not decrease in size following catheterisation. Disorders in micturition are frequent and are almost always in the form of dysuria which may be either slight or severe since the excluded bladder becomes deformed causing obstruction to its neck and the posterior urethra. There is never more than 1 urethra, which is a characteristic finding of this type of malformation.

Both in the case reported by Abrahamson and in the present case, crises of abdominal pain were observed. Examination of the external genitalia may reveal associated malformations and frequently anomalies in the anus and rectum as well as in the entire digestive system. In some instances, blood investigations reveal chronic renal failure of slight or severe degree.

The urographic pattern is characterised by functional exclusion of the kidney, the ureter of which opens into the excluded bladder. There is also often hydronephrosis of the opposite kidney.

The true bladder has a specific appearance, inasmuch as it seems to be displaced and misshapen due to pressure from the excluded bladder. In retrograde cystography the contrast medium is naturally injected only into the bladder connected to the outside. Voiding cysto-urethrography reveals either compression or stretching of the bladder neck or of the urethra.

At cystoscopy the medial wall may appear slightly or even severely deformed and therefore the bladder is considerably distorted, being either elongated or squashed, depending upon the pressure from the other bladder. Only one ureteral orifice is visible.

The diagnostic criteria mentioned are not always paradigmatic and may vary according to the age at which the patient comes to the attention of the physician. The signs which may indicate the presence of a bladder with a complete sagittal or frontal septum are: disorders in micturition, especially dysuria; the presence of an abdominal mass which is not reduced by bladder catheterisation; and functional exclusion of a kidney.

As far as surgical treatment of the double bladder with complete sagittal septum is concerned Abrahamson proposed 3 alternatives:

1. Connecting the 2 bladders by complete resection of the septum.
2. Removing the excluded bladder, leaving the septum, if this is thick and muscular.
3. Removing the excluded bladder with the entire septum and reconstructing the bladder suturing the residual gap.

Nephro-ureterectomy of the excluded kidney should be performed in all cases.

Simple resection of the septum has been performed by Abrahamson and more recently by Levallois and Fontaine. The results cannot be evaluated in the first case because of the early death of the patient but postoperative observations in the second patient confirmed satisfactory function of the bladder following this procedure. In our opinion it is possible with this type of surgical procedure to create a bladder which is too large and is functionally inadequate. It is in fact very difficult during surgery to evaluate the contraction capacity of the detrusor of the excluded bladder, since congenital or acquired structural changes may have severely and irreparably damaged its functional properties.

In the case reported here the third of the procedures outlined was chosen. Simple resection of the septum was not carried out for the reasons mentioned earlier, neither was it considered suitable to leave it as a wall of the residual bladder.

Follow-up and histological studies performed on the excluded bladder and on the septum confirmed the rationality of the procedure chosen. A marked change was observed in the muscle components which were separated and extensively replaced by fibrous connective tissue.

These changes were even more evident in the septum, the muscle tissue of which had been almost entirely replaced by scar tissue. In contrast, in the true bladder, the muscle component is not only preserved but also has a hypertrophic appearance with bands in regular arrangement of considerable thickness.

In such a situation, to leave the complete bladder, removing only the septum, or to leave the latter as wall for the true bladder would almost certainly severely compromise the function of the bladder and would probably lead to the creation of a diverticular sac with no contracting capacity.

Summary

A case of double bladder with complete sagittal septum in which the excluded bladder and septum were removed (together with the silent kidney and ureter) is described.

Long-term follow-up has confirmed the success of the operation.

Cases of this rare malformation reported in the literature are reviewed and diagnosis and therapy are discussed.

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The Nature of the Abnormality in Bladder Neck Obstruction

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There is no dispute that there exists, in men, a condition of obstruction at the bladder neck in the absence of fibrous stricture or prostatic enlargement. The condition was clearly described by Guthrie (1836) and Young (1913) reported the results of his punch resection operation in over 50 cases. The large measure of success now achieved following resection of the bladder neck in these patients has perhaps been allowed to mask our ignorance of the nature of the abnormality and thus discourage studies of its cause. It is perhaps most often thought to result from fibrosis but a number of studies—for example Badenoch (1949)—have shown no associated increase in fibrous tissue. Certainly the condition is in no way similar to the hard fibrous stricture seen more often in the distal urethra, or at the bladder neck as an occasional complication of prostatectomy.

Our study shows that the obstruction is functional in nature and is due to the tightening of the bladder neck as the detrusor contracts.

Method

In this department patients presenting with symptoms compatible with obstruction but without prostatic enlargement, residual urine or gross trabeculation, are further assessed by a method of combined synchronous cine/pressure/flow cysto-urethrography. In this technique, which has been described in detail in an earlier communication (Bates, Whiteside and Turner-Warwick, 1970) pressure-flow values are measured during the course of a routine cinecystogram. The bladder pressure is measured via a fine 1 mm pressure catheter, the abdominal pressure via a similar catheter in the rectum and the flow rate by measuring the rate of change of height of the urine as it is collected in a measuring cylinder, after the manner of von Garrelts (1957). The rectal pressure is subtracted electrically from the total bladder pressure to give an estimate of the intrinsic bladder or detrusor pressure. The paper record of these values is viewed by a second television camera, with attached mixing facilities, so that the pressures and flow rate are superimposed on the image of micturition (Fig. 1). The combined picture is recorded on video tape and reviewed at combined weekly meetings between radiologists and clinicians. By thus visualising whether or not the bladder neck opens freely during voiding, and at the same time assesses the dynamics of voiding, the patients have been separated into 2 contrasting groups, unobstructed and obstructed at the bladder neck. The criteria for this classification are discussed below.

In a small series of these patients (13 unobstructed) we have recorded the urethral pressure profile in the supine position, after the manner of Brown and Wickham (1969). In this technique fluid is run into the bladder from a high reservoir at about 2 ml/min through a 12F or 14F catheter with closed end. The fluid escapes from small side holes arranged in a line around the circumference, near the tip. Attached to a side arm from this catheter is a pressure transducer. With the catheter in the bladder the transducer will at first measure the bladder pressure. As it is withdrawn the pressure will rise until it just overcomes the closing pressure of the urethra and fluid again escapes. Thus, if the pressure is measured as the catheter is slowly removed a trace will

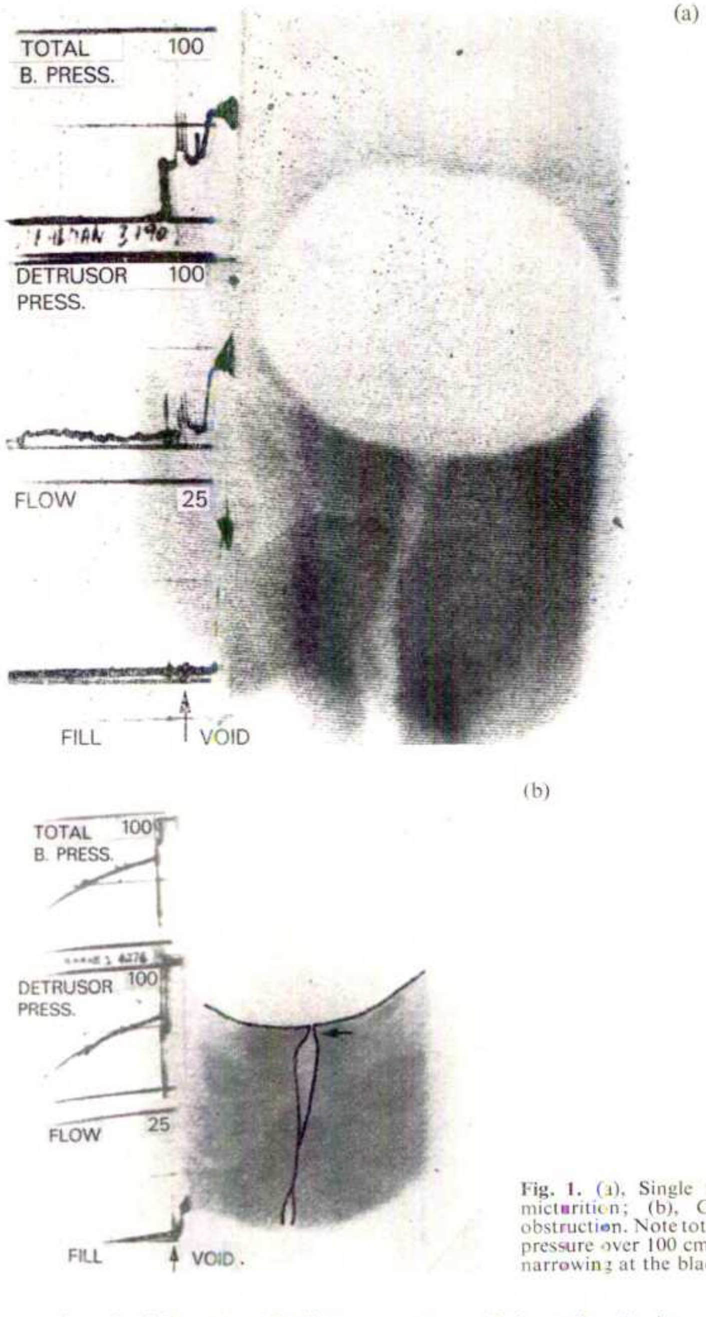

Fig. 1. (a), Single frame of cine record showing normal micturition; (b), Contrasting situation in patient with obstruction. Note total bladder pressure and intrinsic detrusor pressure over 100 cm H_2O and flow rate only 6 ml/sec, with narrowing at the bladder neck.

be produced of first the bladder pressure and then the closing pressure along the length of the resting urethra, when it is dilated to the size of the catheter (Fig. 2).

In this way we can compare the closing pressure of the bladder neck at rest with the detrusor pressure during micturition in obstructed and unobstructed patients and so determine whether the mechanical properties at rest can account, unchanged, for the obstruction during voiding, or whether some functional change occurs.

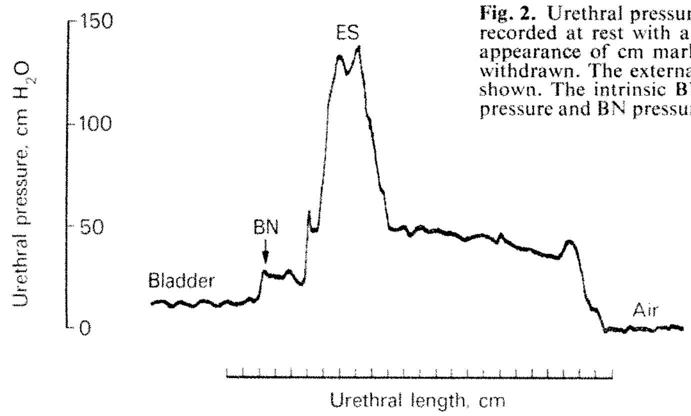

Fig. 2. Urethral pressure profile of a male in the obstructed group, recorded at rest with a 12F catheter. The length scale records the appearance of cm marks at the external meatus as the catheter is withdrawn. The external sphincter (ES) and bladder neck (BN) are shown. The intrinsic BN pressure (the difference between bladder pressure and BN pressure on this profile) is 17 cm H_2O.

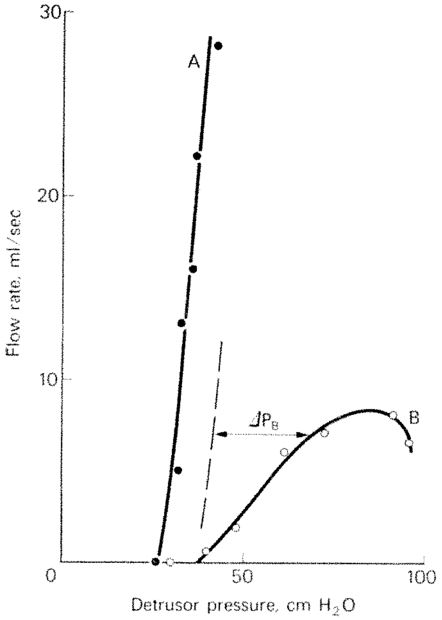

Fig. 3. (A), Graph of flow rate against detrusor pressure (*i.e.*, the urethral resistance relation) for the micturition of a male in the unobstructed group; (B), Similar graph for a male obstructed at the bladder neck. This is the same patient whose urethral pressure profile is shown in Fig. 2. Note that the peak detrusor pressure is 96 cm H_2O, far exceeding the intrinsic BN pressure measured at rest (17 cm H_2O). The broken curve shows part of the urethral resistance relation that might be expected in this patient in the absence of the obstruction (cf. A). For explanation of ΔP_B see appendix.

Measurements during micturition

Clinical material. The series of 26 patients consists of 2 groups of 13, classified as follows: (*a*) Unobstructed—voiding detrusor pressure less than 55 cm H_2O, peak flow rate over 15 ml/sec, bladder neck widely open; (*b*) Obstructed at the bladder neck—voiding peak detrusor pressure over 70 cm H_2O, flow rate less than 10 ml/sec, with narrowing at the bladder neck (compare Figs. 1, A and 1, B). The ages of those in group (*a*) range from 17 to 65 years, with a mean of 37 years. The ages in group (*b*) range from 33 to 70 years, with a mean of 47 years.

Voiding peak detrusor pressure. For each patient the voiding peak detrusor pressure (with abdominal pressure subtracted) has been noted. Its mean value and standard deviation are given in Table I for each group of patients. There is of course a large difference between the two mean values.

Table I.

Mean values and standard deviations of the intrinsic BN pressure at rest and the peak intrinsic detrusor pressure during micturition for 13 unobstructed and 13 obstructed males.

	Unobstructed	Obstructed
Intrinsic BN pressure at rest (cm H_2O)	19 ± 10	27 ± 13
Peak intrinsic detrusor pressure during micturition (cm H_2O)	42 ± 9	93* ± 19

* Possibly an underestimate since some very high values were off-scale.

Urethral Resistance Relation. For each patient's micturition a graph of successive pairs of simultaneous values of flow rate and intrinsic detrusor pressure has been plotted. The curve which is traced out may be interpreted as the urethral resistance relation, governing the rate of flow for a given bladder pressure (Griffiths, 1973). The shape of the curve is totally different for the 2 groups.

For the unobstructed patients the curve is as in Figure 3A, rising very steeply from zero flow rate, with an average slope of between 0·8 and 2 ml/sec/cm H_2O. This means that the detrusor pressure changes very little as the flow rate varies during micturition. It is characteristic of the normal, yielding, non-rigid urethra (ibid.).

For the obstructed patients the relation typically is more curved, as in Fig. 3B, and much less steep. In every case but one the average slope is between 0·05 and 0·25 ml/sec/cm H_2O. This means that the detrusor pressure varies much more markedly with flow rate than in the unobstructed group. The mechanical interpretation of this shape is considered in the appendix.

Measurements of Rest

The Urethral Pressure Profile. A typical profile showing the closing pressure along the length of the urethra of a male patient in the resting state is shown in Figure 2. It can be seen that there is a small rise as the catheter enters the urethra, which represents the pressure exerted by the bladder neck (BN) when it is dilated to the diameter of the catheter (12F or 14F, *i.e.*, 4 or 4·5 mm). The intrinsic BN pressure has been taken as the difference between this peak pressure and the resting bladder pressure. Table I shows the means and standard deviations of the intrinsic BN pressure for the unobstructed and obstructed groups. There is a large overlap between the values for patients in the 2 groups and no significant difference between the 2 mean values ($P > 0{\cdot}05$).

Discussion

Outline of the Argument. The lack of any significant difference between the intrinsic BN pressures for the obstructed and unobstructed groups at once suggests that the obstruction must be functional rather than structural. For the intrinsic BN pressure is the pressure needed to dilate the resting bladder neck to a diameter of 4 to 4·5 mm, which is certainly wider than that of an obstructive BN during voiding (see below). So the obstructive BN is being stretched in this measurement beyond its size during voiding. If the obstruction were structural, one would naturally expect a higher pressure to be needed than for a non-obstructive BN, which is less stretched.

The nature of the functional abnormality may be deduced as follows. At rest, the pressure needed to dilate an obstructive BN to a wide diameter is quite low. During micturition, the pressure available to dilate it is much higher (essentially the detrusor pressure). Yet this high pressure dilates the obstructive BN only to a much narrower diameter (otherwise there would be no obstruction). Therefore the obstructive BN must be tighter during micturition than at rest.

We shall examine the stages of this argument in more detail.

The Diameter of the Bladder Neck during Micturition. In the obstructed group all the cinecystograms necessarily show a narrow bladder neck, so narrow that it is difficult to estimate the diameter at all accurately. However, it is clearly always less than 4 mm, probably very much less.

The diameter is more easily estimated hydrodynamically. The appendix shows that the characteristic shape of the obstructed urethral resistance relation (Fig. 3B) may be understood if, during voiding, the obstructive BN acts as a nozzle of approximately constant diameter. The estimated diameter ranges from 1 mm (3F) to 2·8 mm (8F) with a mean of about 2 mm (6F). The degree of obstruction varies sharply with diameter and is absolutely negligible if the diameter is as great as 4 mm.

Therefore, both visually and hydrodynamically, the diameter of the obstructive bladder neck during micturition is certainly less than the diameter (4 or 4·5 mm) of the catheter used to measure the intrinsic BN pressure at rest.

Comparison of Pressures at Rest and during Micturition. For every obstructed patient the peak intrinsic detrusor pressure during micturition is far greater than the intrinsic BN pressure at rest (compare Fig. 3B with Fig. 2), as is shown by the very large and significant difference between the mean values in the right-hand column of Table I. At rest an intrinsic pressure of 27 ± 13 cm H_2O is sufficient to dilate an obstructive BN to a diameter of 4 to 4·5 mm. During micturition, the pressure available to dilate the BN to this same diameter is far larger, very close to the detrusor pressure, 93 ± 19 cm H_2O (see appendix); yet, as we have seen, the obstructive BN is dilated only to a smaller diameter, about 2 mm, by this higher pressure. Therefore the mechanical properties of the obstructive BN must be different at rest and during micturition: it is clear that the BN becomes tighter during micturition.

This conclusion does not support the commonly held view that obstruction is caused by a partial failure of detrusor tension to pull open the proximal urethra. If it were so caused, the bladder neck would be *less* tight during micturition than at rest (or possibly of unchanged tightness in the most severely obstructed cases).

To summarise, the pressure exerted at rest by an obstructive bladder neck is too low to explain its resistance to dilation by the high pressures generated during voiding and so it must tighten on micturition. This functional change, presumably associated with the contraction of the detrusor, is the source of the obstruction.

Appendix

Intrinsic BN Pressure. Since both bladder and bladder neck are subject to abdominal pressure one should use intrinsic pressures (with abdominal pressure subtracted) in comparing them.

Suppose that the BN pressure at rest is measured with a catheter of diameter d_0. Suppose also that during micturition the intrinsic detrusor pressure is P_B and the volume flow rate is Q. The fluid density is ρ. Then, if the BN diameter during micturition were equal to d_0, the intrinsic fluid pressure there would be equal to $P_B - 8\rho Q^2/\pi^2 d_0^4$. The expression subtracted from P_B is a kinetic energy correction which arises from the Bernoulli equation (Griffiths, 1971). Since the correction never exceeds about 2 cm H_2O for the obstructed group, this pressure, which is that available to dilate the BN to diameter d_0, is very close to P_B itself. A more detailed theoretical treatment will be given in a forthcoming publication (Griffiths, to be published).

Urethral Resistance Relation. The loss (ΔP_B) of pressure head at an obstructive BN which acts as a nozzle of diameter d is very approximately $8\rho Q^2/\pi^2 d^4$. It is significant (*i.e.*, more than 5 cm H_2O for $Q = 10$ ml/sec) only if d is less than about 3·6 mm.

The loss ΔP_B shifts the urethral resistance relation to higher pressures (compare the broken curve with curve B in Fig. 3). If d remains approximately constant during micturition then ΔP_B is proportional to Q^2 and so a flatter, curved urethral resistance relation results, as observed (Fig. 3B). Hence, from such a urethral resistance relation, d^4 may be roughly, and d itself more accurately, estimated.

The fact that the obstructed urethral resistance relation corresponds to an approximately constant BN diameter, independent of variations in P_B, means that during micturition the BN behaves as a near-rigid nozzle: *i.e.*, a very high pressure would be needed to dilate it beyond the diameter d. Yet at rest it is very distensible: *i.e.*, it is easily dilated to the larger diameter d_0. This again shows the functional change in mechanical properties.

Summary

We have compared the pressure exerted by the bladder neck at rest with the bladder pressure generated during micturition in a series of 26 male patients, 13 unobstructed and 13 obstructed at the bladder neck.

We find that the degree of obstruction caused by a bladder neck cannot be determined from the pressure it exerts at rest and that this pressure is too low to explain the resistance of the obstructive bladder neck to dilation by the high pressures generated during voiding. It follows that the obstruction is functional in nature and is caused by a tightening of the bladder neck during micturition.

In addition, we find that shape of the urethral resistance relation is quite different in unobstructed and obstructed patients and deduce that, during micturition, an obstructive bladder neck forms a narrow nozzle of approximately constant diameter, usually about 2 mm (6F).

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The Influence of Vesical Distension on Urethral Resistance to Flow: the Collecting Phase

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In the course of the filling of the urinary bladder an increase in the urethral pressure was observed by several investigators (Karlson, 1953; Tanagho *et al.*, 1966; Griffith, 1973; Glenn, 1974).

Earlier works by Elliot (1907) and Denny-Brown and Robertson (1933) could provide an explanation for these changes. They reported the presence of a functional internal sphincter and that there is a reciprocal innervation between the detrusor and internal sphincter. Accordingly, as a result of detrusor stretch during the collecting phase of the voiding cycle, there is a reflex increase in the tone of the internal sphincter.

However, these early concepts were seriously challenged by the anatomical findings of Woodburne (1960) and of Tanagho and Smith (1966). These studies have demonstrated the absence of an anatomical internal sphincter and that the detrusor muscle and the urethra form one continuous sheet of muscle. On this basis Lapides (1958) and Tanagho *et al.*, (1966) maintain that, with increasing vesical distension, tension is transmitted to the urethral wall resulting in a more effective closure.

Gilmore and Vane (1971) demonstrated that catecholamines are released into the circulation as a result of vesical distension. It is not unreasonable to suggest that the released catecholamines induce an increase in the urethral resistance to flow, through stimulation of α-adrenergic receptors in the urethral wall or its vascular bed.

A modification of Brown and Wickham's technique (1969) for recording the urethral pressure profile provides an accurate and a reproducible method for measurement of urethral resistance to flow. In a series of experimental studies using dogs this technique was utilised to analyse the changes of urethral resistance in response to vesical distension and to define their underlying mechanisms.

Material and Methods

Preparation of the Animals. 14 female mongrel dogs, weighing between 10 and 12 kg, were used in a total of 20 experiments. The dogs were anaesthetised with intravenous chloralose (5 gm of chloralose, 60 gm of urethane in 75 ml of propylene glycol). An initial dose of 1·5 ml/kg was injected; small additional doses were given as required. The trachea was intubated and respiration was mechanically controlled at a rate of 14 to 16 respirations/min. An intravenous infusion of normal saline was started in a forearm vein. An episiotomy was performed to allow easy access to the urethra. The bladder was catheterised and emptied at the start of the experiment and before each set of measurements.

A cannula was then placed through one femoral artery and its tip was guided to the junction of the iliac arteries and the abdominal aorta. This cannula was used for injection of drugs and monitoring the blood pressure.

In 4 dogs a second cannula was inserted into the peritoneal cavity through a puncture in the iliac fossa for recording changes in the intra-abdominal pressure.

The Recording System. The arterial blood pressure and the intra-abdominal pressure were measured via the two cannulae connected to pressure transducers (Type M.P.L.S. 125, Kulite Semi-conductor Producers Inc. N.J.) and the signal recorded on a multichannel recorder (Model 2106 Visicorder, Honeywell, Colorado).

The technique for measurement of the urethral pressure profile was described in detail in a previous publication (Ghoneim *et al.*, 1975). The profile was recorded on an X-Y recorder (Type 7004B, Hewlett-Packard, Mass.).

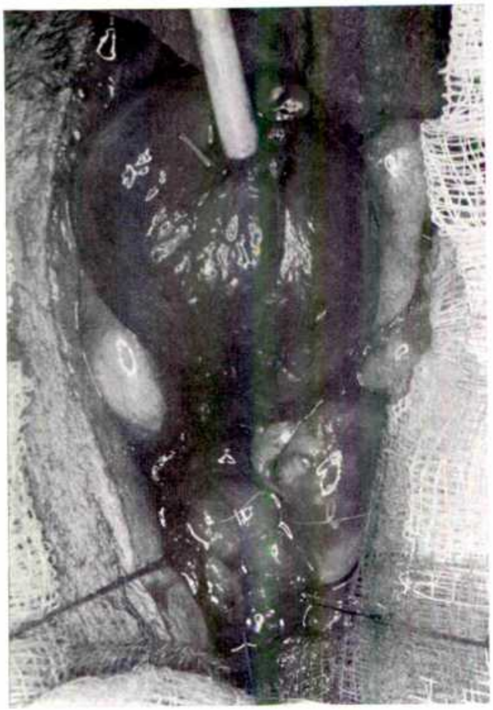

Fig. 1. The bladder is separated from the trigone and urethra. A catheter is inserted into the dome of the bladder for filling and monitoring the intravesical pressure.

This arrangement allowed the simultaneous recording of the urethral resistance to flow (Y input) and the displacement of the urethral catheter (X input).

The Experimental Protocol. (1) After administration of anaesthesia a waiting period of 1 hour was allowed for stabilisation. This was followed by several recordings of the resting urethral pressure. 30 to 50 ml increments of saline were slowly injected into the bladder via the profile catheter and a measurement of urethral pressure was recorded after each additional filling. The process was repeated till the onset of spontaneous voiding.

(2) The same procedure was repeated after the intra-arterial injection of the following agents; each dog serving as its own control:

(*a*) Pentolinum tartarate (Ansolysen—May & Baker Ltd.) in a dose of 3 mgm/kg: 4 dogs.
(*b*) Phentolamine mesylate (Rogitine, Ciba Co. Ltd.) in a dose of 1 mgm/kgm: 3 dogs.
(*c*) Succinyl choline (Anectine, Burroughs Wellcome & Co.) in a dose of 1 mgm/kgm: 3 dogs.

(3) In 4 dogs the bladder was exposed through a midline incision and a balloon inserted into its cavity through a small incision in the bladder dome. The balloon was distended by fluid and the urethral pressure profiles were recorded as above.

(4) In 6 dogs after recording the resting pressure and the urethral response to increasing vesical distension, the bladder was exposed by a midline incision. The bladder was then surgically separated from the trigone. The line of section was just above the level of the insertion of the ureters (Fig. 1). The trigone was left open while the incision in the bladder was meticulously closed in 2 layers, using fine catgut. A cannula was inserted in the dome of the bladder and secured in place by a purse-string suture. The bladder was gradually distended through this cannula and the urethral pressure was recorded after each additional filling.

Results

General Observations. As a result of vesical distension a series of consistent changes were observed in the urethral pressure profile (Fig. 2). With bladder filling there was an increase in the intravesical pressure, accompanied by a higher increase in the urethral pressure. These changes were more pronounced in the distal segment of the urethra. Immediately before the onset of voiding there

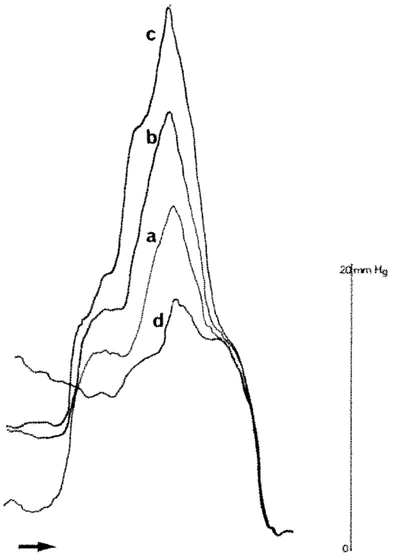

Fig. 2. Influence of gradual vesical distension on urethral pressure profile; a. empty bladder; b. 30 ml in bladder; c. 60 ml in bladder; d. 100 ml in bladder.

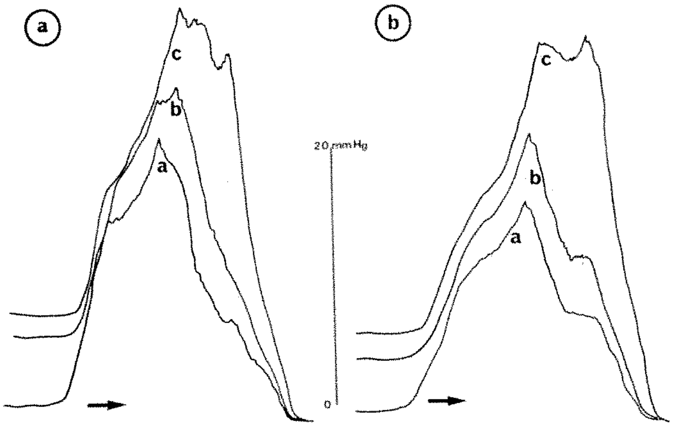

Fig. 3. Influence of pentolinium on the changes in the urethral pressure profile during the collecting phase; (a) before pentolinium,
a. empty bladder,
b. 40 ml in bladder,
c. 80 ml in bladder;
(b) after pentolinium.

was a marked reduction of the amplitude of the profile to a level below that of the intravesical pressure. The same sequence of events could be reproduced when detrusor distension was achieved by filling the intravesical balloon. Moreover, these changes did not reflect any variations of the intra-abdominal pressure when it was recorded simultaneously by the intraperitoneal catheter.

Influence of Pentolinium. In general, following the administration of the ganglion blocking agent, there was some reduction in the amplitude of the resting profile. Nevertheless, the changes in urethral pressure in response to vesical distension were qualitatively the same; in other words there was a gradual increase in the urethral pressure during the collecting phase (Fig. 3).

Influence of Succinyl Choline. After the injection of the neuromuscular blocking agent the pronounced increase in the urethral pressure of the distal segment of the profile was obliterated. However, the increase in the proximal segment was not significantly changed (Fig. 4).

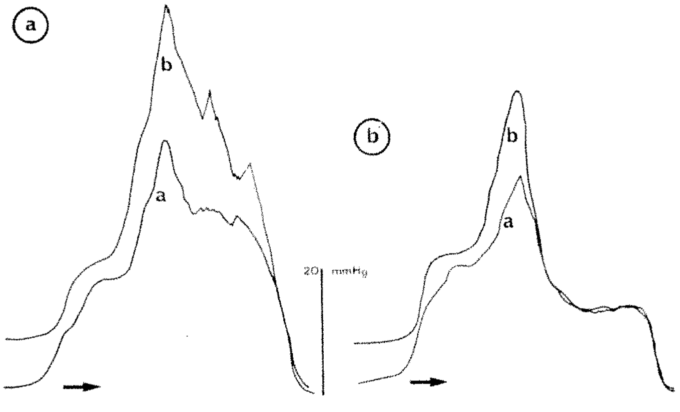

Fig. 4. Influence of succinyl choline on the changes in the urethral pressure profile during the collecting phase;
(a) before succinyl choline,
a. empty bladder,
b. 60 ml in bladder;
(b) after succinyl choline.

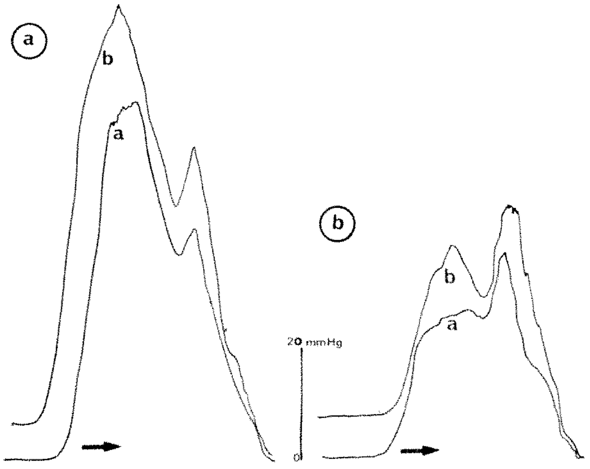

Fig. 5. Influence of phentolamine on the changes in the urethral pressure profile during the collecting phase;
(a) before phentolamine,
a. empty bladder,
b. 50 ml in bladder;
(b) after pentolamine.

Influence of Phentolamine. There was a significant reduction of the resting pressure of the urethra involving all segments of the profile. Nevertheless, the increase in pressure recordings with vesical distension was maintained but on a smaller scale as compared to that of the controls (Fig. 5).

Influence of Vesico-urethral Interruption. Remarkable changes in the urethral response to vesical distension were noted following this procedure. Instead of having an initial increase the profile tracings remained unchanged or a reduction in the amplitude was recorded. With increasing distension further reduction in the urethral pressure was noticed. This reduction was linear and proportionate to the degree of vesical distension until a certain limit, beyond which no further reduction could be obtained. These changes involved both the proximal and the distal segments of the profile (Fig. 6).

Discussion

These experiments have demonstrated that changes in the urethral pressure, in response to vesical distension, follow a certain sequence. During the collecting phase there is a gradual increase in the urethral pressure. This increase is higher than the rise of the intravesical pressure and is more pronounced in the distal segment of the urethra. During the expulsion phase there is

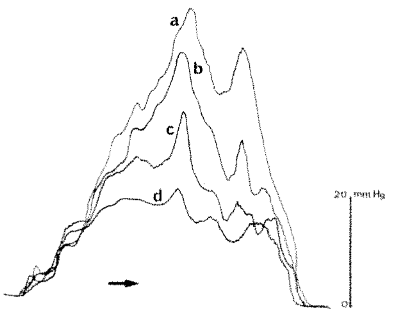

Fig. 6. Influence of vesico-urethral interruption on the urethral pressure profile during vesical distension; a. empty bladder; b. 30 ml in bladder; c. 60 ml in bladder; d. 90 ml in bladder.

a reduction in urethral pressure which involves both the proximal and distal segments of the urethra.

There was no correlation between the changes in the urethral pressure and variations in the intra-abdominal pressure when both were recorded simultaneously. Moreover, reproduction of these changes by distending the intravesical balloon excludes the possibility of an experimental error which may result from a leak from the bladder of the anaesthetised dog into the urethra, thus leading to a false increase in resistance to flow.

Blockage of the autonomic ganglia by pentolinium did not interfere with such an increase, which clearly shows that these changes are not mediated through an autonomic reflex. This finding, coupled with the fact that vesico-urethral interruption prevented any increase of urethral pressure, provides strong evidence that these changes are the result of mechanical stretching of the urethral muscles secondary to vesical distension. This is in agreement with the contentions of Lapides (1958) who maintains that with increasing vesical distension and due to muscle continuity tension is transmitted to the urethral wall resulting in an increased resistance to flow. In addition, tissue tension created by the fasciae and striated muscles immediately surrounding the urethra contributes to the increased resistance observed in the distal part of the urethra (Tanagho *et al.*, 1966).

Paralysis of striated muscle by succinyl choline markedly diminished the increase of pressure in the distal segment of the urethra. This was also reported by Tanagho, Meyers and Smith (1969); a fact which emphasises the contribution by the striated muscles to the intra-urethral pressure of this segment. Nevertheless, the urethral closing pressure was adequate to maintain continence. This is in agreement with the studies of Lapides (1957) and with the clinical observation that continence could be preserved after pudendal neurectomy.

Following the administration of phentolamine there was a significant drop in the resting pressure of the urethra involving its proximal and distal segments. This finding demonstrates that α-adrenergic activity is responsible—at least in part—for the urethral resistance to flow at rest. Nevertheless, blocking of the α-adrenergic receptors did not interfere significantly with the increase of the amplitude of the profile in response to vesical distension. This indicates that the increase of urethral pressure during the collecting phase does not reflect a significant enhancement of α-adrenergic activity.

Conclusions

1. During the collecting phase there is an increase in urethral resistance to flow, which is more marked in the distal segment of the urethra.

2. This increase is not mediated through an autonomic reflex and does not reflect a significant enhancement of α-adrenergic activity.

3. It is essentially due to stretching of the urethral muscle, secondary to vesical distension.

Summary

Using female dogs, changes in the urethral pressure profile in response to vesical distension were studied. It was noted that during the collecting phase there was an increase in the amplitude of the profile tracing.

These experiments revealed that this increase is not mediated through an autonomic reflex and does not reflect a significant enhancement of α-adrenergic activity. These changes are mainly due to increased tension of the urethral muscle, secondly to detrusor stretch.

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The Influence of Vesical Distension on Urethral Resistance to Flow: the Expulsion Phase

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Urine is retained in the bladder as long as the closure pressure, the difference between the maximal intra-urethral pressure and simultaneously existing bladder pressure, remains above zero (Enhörning, 1961). For micturition to start, this closure pressure must first drop and become negative.

There are several diverging concepts regarding the mechanisms involved in the process of initiation of voiding. Working with cats, Barrington (1931) reported that distension of the bladder or active contraction of its wall induced a reflex relaxation of the urethra. Similar findings were later reported by Langworthy, Drew and Vest (1940) and Girado and Campbell (1959).

On the basis of his experimental and clinical studies, Lapides (1961) contends that the bladder body contracts down upon the bolus of urine pulling open the bladder neck. Moreover, contractions of the longitudinal muscles of the bladder and urethra result in shortening of the urethra, widening of its lumen and reduction of its resistance to flow. A similar mechanical approach was suggested by Hutch (1965). He believes that active detrusor contraction precedes voiding. As a result of this contraction the base plate moves out of its flat position into a cone one; the bladder neck is thus opened and voiding starts.

Muellner (1958) postulated that in man voluntary relaxation of the pelvic floor permits the descent of the vesical neck. This descent is the stimulus for the detrusor to contract initiating voiding. Tanagho and Miller (1970) also reported that prior to voiding there is a drop of the intra-urethral pressure as a result of relaxation of the pelvic floor and the striated external sphincter. However, they provided evidence showing that this is dependent on an involuntary reflex activity which is synchronised to precede detrusor contraction.

Jonas and Tanagho (1974) introduced an elegant experimental model for the study of the urethral response to detrusor stretch. Using dogs, the body of the bladder was surgically separated from the trigone and urethra. Accordingly, it was possible to record the intravesical and intra-urethral pressures simultaneously, eliminating the factors of direct muscular continuity or the hydraulic effect of the bolus of urine.

Using a similar experimental model we report here our studies on the influence of vesical distension of the urethral pressure profile. Our objective was to characterise these effects and define the various mechanisms that may be involved in their evolution.

Material and Methods

Preparation of the Animals. 30 female mongrel dogs, weighing between 10 and 12 kg, were used. The dogs were anaesthetised with intravenous chloralose (5 g of chloralose, 60 g of urethane, in 75 ml of propylene glycol). An initial dose of 1·5 ml/kg was injected; small additional doses were given as required. The trachea was intubated and respiration was mechanically controlled at a rate of 14 to 16 respirations/min. An intravenous infusion of normal saline was started in a forearm vein. An episiotomy was performed to allow easy access to the urethra. The bladder was exposed by a midline incision. Then, the trigone was surgically separated from the bladder body. The line of section was just above the level of the ureteric insertions. Great care was exercised to avoid injury of the blood or nerve supply to either compartments. The trigone was left open, while the incision in the bladder was meticulously closed in 2 layers, using fine catgut. A cannula was inserted in the dome of the bladder and secured in place by a purse-string suture. This was used for filling the bladder and measurement of the intravesical pressure.

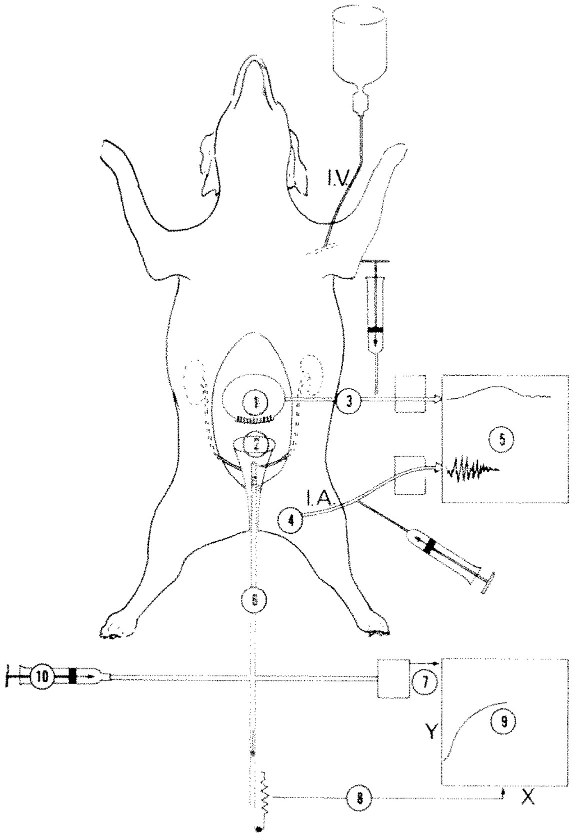

Fig. 1. Diagram of the experimental model and assembly of the recording system.
1. Body of bladder. 2. Trigone and urethra. 3. Catheter for bladder filling and monitoring intravesical pressure. 4. Cannula in femoral artery. 5. Multichannel recorder. 6. Profile catheter. 7. Transducer feeding Y input of X-Y recorder. 8. Variable electric tension feeding X input of X-Y recorder. 9. X-Y recorder. 10. Constant speed pump.

Another cannula was then placed through one femoral artery and its tip advanced to the junction of the iliac arteries and the abdominal aorta. This cannula was used for injection of drugs and monitoring the blood pressure.

The Recording System. The arterial blood pressure and the intravesical pressure, were measured via the two cannulae connected to pressure transducers (Type M.P.L.S. 125, Kulite Semi-conductor Producers Inc.) and the signals recorded on a multichannel recorder (Model 2106 Visicorder, Honeywell).

The technique for measurement of the urethral pressure was described previously in detail (Ghoneim *et al.*, 1975). The urethral resistance to flow and the displacement of the profile catheter were recorded simultaneously using an X-Y recorder (Type 7004B, Hewlett-Packard).

The final preparation of the animal and the assembly of the recording system are diagrammatically represented in Figure 1.

The Experimental Protocol. After preparation of the animal, a waiting period of 1 hour was allowed. This was followed by several recordings of the resting urethral pressure. 30 to 50 ml increments of warm saline were slowly injected into the bladder; 1 min was then allowed for stabilisation and the intravesical pressure and the urethral pressure profile were recorded. This process was repeated until the bladder was distended to capacity. Finally, the bladder was evacuated and a urethral pressure tracing was recorded.

The procedure detailed above was repeated after the intra-arterial injection of the pharmacological agents listed below. Each dog served as its own control. The bladder was redistended with volumes of fluid equal to those used in the initial study. Final readjustments were sometimes necessary to obtain the same intravesical pressure as that of the control, since this parameter was used as the basis for comparison.

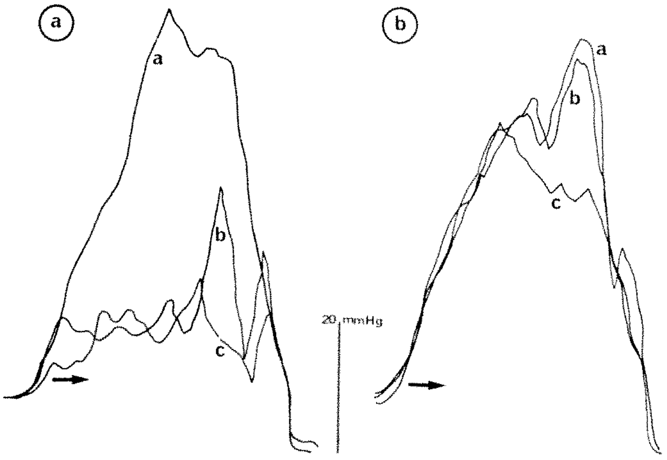

Fig. 2. Influence of pentolinium on the urethral response to vesical distension;
(**a**), Before pentolinium,
a. empty bladder,
b. 40 ml in bladder,
c. 90 ml in bladder;
(**b**), After pentolinium.

The Pharmacological Agents.

1. *Pentolinium Tartarate* (Ansolysen, May & Baker Ltd.)

This was used in a dose of 3 mg/kg in 6 dogs. The efficiency of blockage of the autonomic ganglia was tested by the inability of D.M.P.P. (Dimethyl Phenyl Piparazinium Iodide, Aldrich Chemical Co. Inc.) in a dose of 0·05mg/kg to produce its strong nicotinic stimulating action on the cardiovascular system.

2. *Succinyl Choline* (Anectine, Burroughs Wellcome & Co.)

Neuromuscular transmission was blocked by this agent (1 mg/kg) in 4 animals.

3. *Atropine Sulphate* (Glaxo-Allenburys)

In 4 dogs the muscarinic receptors were blocked by atropine in a dose of 0·1 mg/kg. The blockage was controlled by the failure of bethanechol chloride (Urecholine, Merck Sharp & Dohme) in a dose of 0·05 mg/kg to induce a powerful bladder contraction.

4. *Phentolamine Mesylate* (Rogitine, Ciba, Co., Ltd,)

Alpha adrenergic receptors were blocked by Rogitine (1 mg/kg) in 4 dogs. Failure of levarterenol bitartarate (Levophed, Winthrop), in a dose of 0·01 mg/kg to induce alpha-stimulating effects on the cardiovascular system, was taken as an index of successful blockage.

5. *Propranolol Hydrochloride* (Inderal, Ayerst)

Beta adrenergic receptors were blocked by Inderal (3 mg/kg) in 5 dogs. The efficiency of blockage was indicated by the inability of isoproterenol hydrochloride (Isuprel, Winthrop) in a dose of 0·01 mg/kg to induce the well recognised beta effects on the circulation.

Results

General Observations: With increasing vesical distension there was a reduction in the amplitude of the urethral pressure tracing. This reduction was proportional to the degree of vesical distension, until a certain limit was reached beyond which further reduction was unobtainable. These changes involved both the proximal and distal segments of the urethra. Moreover, when the bladder was emptied of all fluid the urethral pressure regained its resting (pre-distension) value within 1 to 2 min.

Influence of Pentolinium: Following the administration of pentolinium the urethral response to vesical distension was completely blocked. This is clearly demonstrated in Figure 2.

Influence of Succinyl Choline. When neuromuscular transmission was blocked there was a significant reduction of pressure in the distal segment of the urethra. Nevertheless, further reduction was obtained when the bladder was distended (Fig. 3).

Influence of Atropine. Blocking of the muscarinic receptors by atropine did not interfere to any significant degree with the usual pattern of the urethral response to vesical distension (Fig. 4).

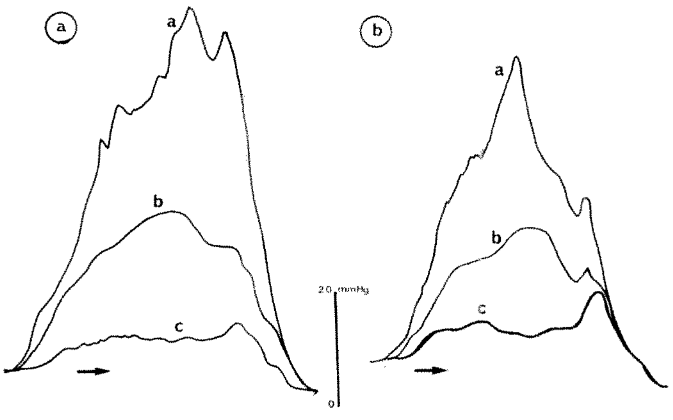

Fig. 3. Influence of succinyl choline on the urethral response to vesical distension;
(a), before succinyl choline;
a. empty bladder,
b. 30 ml in bladder,
c. 60 ml in bladder;
(b), After succinyl choline.

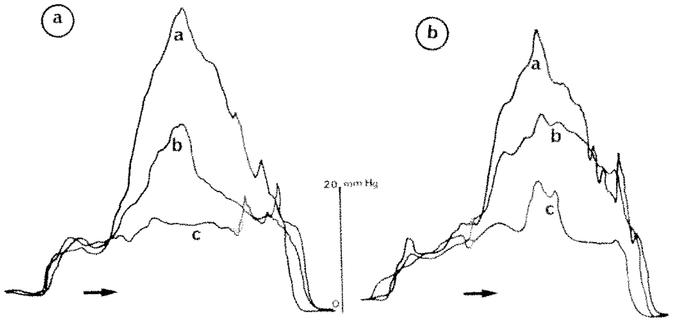

Fig. 4. Influence of atropine on the urethral response to vesical distension;
(a), Before atropine;
a. empty bladder,
b. 30 ml in bladder,
c. 60 ml in bladder;
(b), After atropine.

Influence of Phentolamine. Blocking of the α-adrenergic receptors resulted in a marked reduction of the resting urethral pressure which involved its proximal and distal segments. Subsequent vesical distension failed to induce any further reduction of the urethral pressure (Fig. 5).

Influence of Propranolol: Following blockade of the β adrenergic receptors it was noticed that the urethral response to slight or moderate degrees of vesical distension was effectively obliterated. Nevertheless, with higher degrees of detrusor stretch the urethra still responded by a marked reduction of its resistance to flow (Fig. 6).

Discussion

In a recent critical review Nergardh (1975) proposed an experimental model for the study of autonomic receptor functions in the lower urinary tract. His model consists of an isolated preparation of the bladder outlet region of cats (bladder base, bladder neck and proximal urethra). The specimen was perfused in an organ bath and the response to various autonomic drugs was studied as a function of variation in the resistance to flow. We believe that the model utilised in this study provides several advantages over that of Nergardh. The bladder and urethra are kept *in situ* with their intact vascular and nervous supply, an important requisite for any functional study. The preparation allows simultaneous recording of the intravesical pressure and urethral resistance to flow without the interference of such factors as the direct muscular continuity or the hydraulic effects of the vesical contents. Moreover, Nergardh recorded the total resistance to flow, while urethral pressure profile tracings provide a measurement of pressure at every point along the urethral length. This allows precise definition of the site of action of the pharmacological agent under investigation.

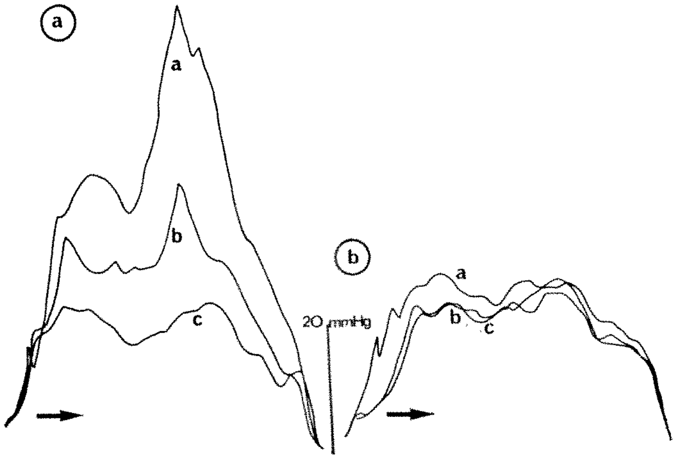

Fig. 5. Influence of phentolamine on the urethral response to vesical distension;
(**a**), Before phentolamine;
a. empty bladder,
b. 30 ml in bladder,
c. 50 ml in bladder;
(**b**), After phentolamine.

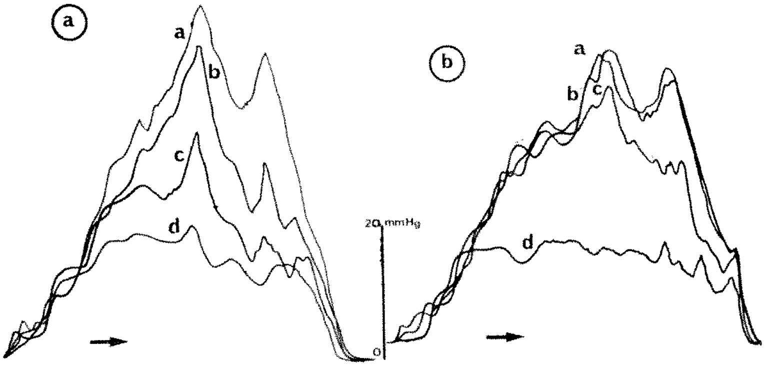

Fig. 6. Influence of propralonol on the urethral response to vesical distension;
(**a**), Before propralonol;
a. empty bladder,
b. 30 ml in bladder,
c. 60 ml in bladder,
d. 90 ml in bladder;
(**b**), After propralonol.

Chloralose was the anaesthetic of choice since it is well known that Nembutal anaesthesia can interfere with reflex activity through its atropine-like cholinergic blockade and sympathetic ganglion depression (Goodman and Gilman, 1970).

Our studies revealed that there is an active reduction of urethral resistance as a result of vesical distension. This reduction does not depend on a muscular continuity or on the hydraulic effects of the bolus of urine. These findings are in agreement with those of Jonas and Tanagho (1975). The ability of pentolinium to block these changes provides an objective evidence that the reduction of urethral resistance is mediated through autonomic ganglia and involves a reflex activity. This supports the earlier studies reported by Barrington (1931), Langworthy *et al* (1940) and Girado and Campbell (1959).

This reflex reduction of urethral resistance involved the proximal and distal segments of the urethra. Paralysis of the striated muscles by succinyl choline reduced the pressure amplitude of the distal part of the profile tracing. Nevertheless, further drop in the urethral pressure was obtainable with vesical distension. In other words, this reflex activity involves both the smooth and striated muscle components of the urethra. Jonas and Tanagho (1975) reported differently. Following the administration of Flaxedil there was no drop in the urethral pressure in response to detrusor stretch. This difference could be explained by the fact that, in addition to its neuromuscular blocking effect, Flaxedil has the ability to block autonomic transmission (Foldes, 1960).

Traditionally it has been believed that the mammalian urethral rhabdosphincter has a purely somatic innervation through the pudendal nerve. However, Gil-Vernet (1964) and Winckler (1966) concluded that the rhabdosphincter in many species, including man, is not innervated by

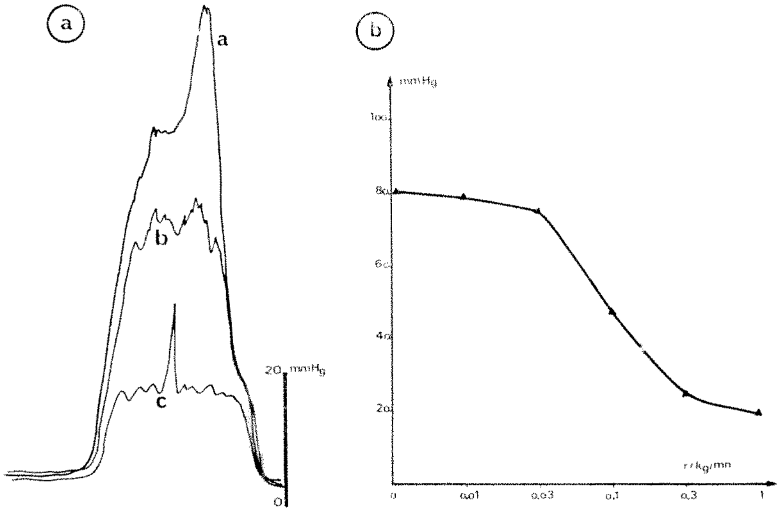

Fig. 7. Influence of isoproterenol (intra-arterial) on the urethral resistance to flow;
(**a**), The urethral pressure profile;
a. resting profile,
b. 0·1 microgram/kgm,
c. 1 microgram/kgm;
(**b**), Dose response curve.

the pudendal nerve but by branches of the pelvic plexus receiving sympathetic and parasympathetic nerve fibres. Elbadawi and Schenk (1974) demonstrated histochemically that the rhabdosphincter receives triple sympathetic—parasympathetic—somatic innervation. Accordingly, in spite of the fact that it is a skeletal muscle the urethral rhabdosphincter is under the control of both divisions of the autonomic nervous system. These studies give a morphological basis to the functional observations that the striated muscle component of the urethra is involved in the reflex urethral response to vesical distension. Furthermore, electromyographic studies of the activity of the perineal muscles during voiding provide additional support to these contentions. Vereecken and Verduyn (1970) have demonstrated that during voiding the activity of all the perineal muscles disappears and that this silent period begins simultaneously with or slightly before the pressure rise in the bladder.

Our observations failed to demonstrate that muscarinic receptors are involved in any significant degree in the reflex reduction of urethral resistance in response to vesical distension. On the other hand, it seems that adrenergic receptors play an important role in the mediation of these changes. The presence of adrenergic receptors in the urethra has been established pharmacologically (Raz and Caine, 1971) and histochemically (Elbadawi and Schenk, 1974). Phentolamine produced a significant drop in the resting urethral pressure; vesical distension could not induce any further reduction. Whether this action is exerted on the plain muscles of the urethral wall (Donker, Ivanovici and Noach 1972; Tulloch, 1974), or on the rich vascular bed of the urethra (Tanagho, Meyers and Smith, 1969), or both (Raz, Caine and Zeigler, 1972), is not the scope of this publication. Accordingly, in agreement with Kleeman (1970) and Krane and Olsson (1973), the inevitable conclusion was made that α-adrenergic activity is responsible—at least in part—for the urethral resistance at rest. Moreover, following the administration of propranolol, reflex reduction of urethral pressure in response to slight or moderate degrees of vesical distension, was effectively blocked. This suggests that these changes could involve activation of β-adrenergic inhibitory mechanisms. Raz *et al.* (1972) demonstrated that isoprenaline produced a marked decrease in the tone of the isolated female canine urethra. This finding is substantiated by our own observations (Fig. 7a and b). Isoproterenol produced a dose-dependent reduction of the urethral pressure profile tracings, which involved its proximal and distal segments. Nergardh (1974, 1975) suggests an attractive mechanism by which beta activity may be enhanced. On the basis of the histochemical studies of Elbadawi and Schenk (1971) he maintains that acetylcholine acting through short adrenergic neurons activates intramural ganglia cells belonging to the sympathetic system. As a result noradrenaline is released at the adrenergic nerve endings. He demonstrated that, in low concentrations, noradrenaline was able to reduce the resistance to flow of the outlet region of cat's bladder through stimulation of beta receptors.

Nevertheless, the inability of beta blocking agents to obliterate the reflex reduction of urethral resistance completely at high degrees of vesical distension strongly suggests the involvement of other mechanisms. The presence of inhibitory non-adrenergic, non-cholinergic neurons in the gut wall has been thoroughly documented (Burnstock, 1972). Ambache and Zar (1970) reported the presence of similar fibres in the wall of the bladder of guinea pigs. Involvement of local mediators such as histamine, 5-hydroxytryptamine and prostaglandins provides another viable explanation. These alternative mechanisms are being explored in a current investigation.

Conclusions

1. Vesical distension leads to a reduction of urethral pressure, which is not dependent on any muscular continuity or on the hydraulic effects of vesical contents.
2. This reduction is mediated through autonomic ganglia.
3. These changes involve both the plain and striated muscles of the urethra.
4. Muscarinic receptors are not involved in this process.
5. Activation of inhibitory β-adrenergic mechanisms is partially responsible for these changes.
6. Other complex mechanisms involving different pathways are also responsible for the mediation of this reflex.

Summary

The influence of vesical distension of the urethral pressure profile was studied in female dogs, using a model in which the bladder and urethra were separated.

There was a reduction in the urethral resistance involving its smooth and striated muscle components. This reduction was completely blocked by ganglion blocking agents. Atropine did not influence these changes. Propranolol could only partially block this reflex.

The other possible mechanisms that could be involved were discussed.

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Suprapubic Prostatectomy combined with Vesico-urethroplasty

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Preservation of the urethra, that is of an epithelialised channel, was implicit in the extraurethral method of enucleation of the prostate but was soon to be fortuitously abandoned for technical reasons (Freyer, 1920). Thus chance and the undisputed gratifying results of the simple enucleative operation conspired towards a general acceptance of an unepithelialised cavity as a worthwhile price for relief of bladder outlet obstruction. An attempt was made many years later to restore an epithelial lining to the prostatic cavity (Harris, 1929) though such cover was only partial through the retention of the posterior urethral epithelium or through re-trigonisation. The subsequent universal introduction of wedge resection of the bladder neck as an additional step in prostatectomy rather devalued the "plastic" concept of the Harris operation and was doubtless instrumental in establishing the doctrine that the prostatic cavity was unsuited to plastic procedures (Swift-Joly, 1932; Harris, 1934).

The writer described briefly in a preliminary report a new method of prostatectomy incorporating an urethroplasty (Magri, 1968). It was shown that restoration of epithelial cover to the prostatic urethra was feasible and that it could contribute towards a further reduction in post-prostatectomy complications which remain unacceptably high following established techniques (Leadbetter, Duxbury and Leadbetter, 1959; Marshall, 1967). Over 400 patients have now been treated and it is the purpose of this paper to describe and illustrate in fuller detail the steps in the operation and to present the results of the enlarged series.

The Premise

Figure 1 depicts in diagrammatic form the principles involved in the new technique and in the fashioning of the bladder flaps and their subsequent deployment. A transverse incision in the capsule coupled with a vertical incision which extends proximally into the bladder outlines two triangular epithelialised flaps, AFC and BGC. As the constricting bladder neck is thus completely divided, the traditional excision of the bladder neck posteriorly can safely be omitted and the posterior urethral wall will be left intact. The remaining "bare" area of the prostatic cavity is re-covered by advancing point "C" on the bladder wall within the prostatic capsule to point "C_1" at which lies the partially severed urethra. This manoeuvre, facilitated by the usually good mobility of the bladder, locates the flaps alongside the preserved urethral wall to line the lateral aspects of the prostatic cavity, while the anterior surface will be covered by that part of the bladder wall which lies proximal to the vertical component of the incision (CDE).

The Operation

Anaesthesia. No uniform technique was adopted. Hypotensive anaesthesia, by which is meant the planned controlled reduction of the systolic blood pressure to 70 mm Hg or lower was employed in about a third of the cases.

Technique. A Pfannenstiel incision is used and the vas ligated within the pelvis. Retraction of the wound edges is achieved by the combined use of a modified Kilpatrick retractor and a Joll thyroid retractor.

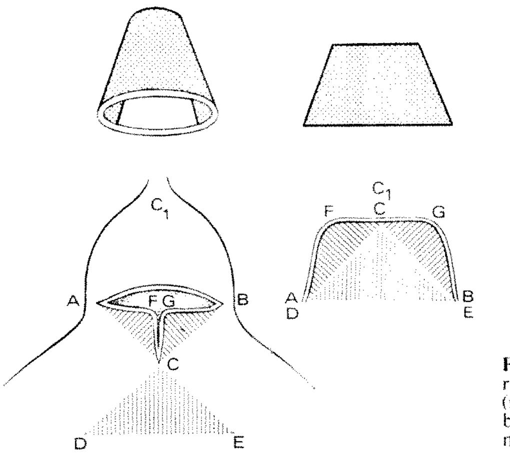

Fig. 1. *Top*: Prostatic urethra after enucleation diagrammatically represented as a truncated cone (left) with unepithelialised area (stippled) laid out flat (right). *Bottom*: showing flaps as developed by T-incision (left) and following re-alignment through advancement (right).

The anterior surface of the prostatic capsule is exposed after coagulation and division of the pre-prostatic veins. A transverse incision is made in the prostatic capsule between 2 stay sutures, capsular bleeding being controlled by coagulative diathermy. The plane between the adenomatous enlargement and the capsule is identified and careful separation is performed digitally on the anterior and lateral aspects of the prostate with no attempt at enucleation. The bladder is next entered at the level of the internal urethral meatus using scissors, the opening being enlarged laterally, thus separating anterior bladder wall and proximal capsule from the prostatic "adenoma".

The vertical component of what will in fact become an inverted T-shaped vesico-capsular incision is now added (Fig. 2). A spreader is inserted which, held in the operator's left hand, keeps the proximal capsule and bladder neck taut while an assistant exerts gentle tension on the anterior bladder wall with a sponge on a holder. Starting at the mid-point of the transverse incision and using a cutting diathermy current, an incision is made which cuts across the palpably constricting bladder neck and is extended proximally until all the constricting fibres have been severed. This point is recognized by the sudden "give" which is seen and felt as the now normal resilient bladder wall "flows" easily over the limbs of the spreader. The proximal limit of this incision is dictated by the size of the bladder wall flaps required and indirectly therefore by the area of prostatic bed that needs to be re-lined. The sclerotic tissue at the bladder neck retracts towards the corners of the original capsular incision and can be trimmed away with advantage in those cases in whom it is particularly exuberant to facilitate the in-turning of the flaps during the reconstruction.

The next step in the operation is the removal of the adenomatous enlargement. The anterior commissure binding the two lobes together is divided with scissors down to a level opposite the verumontanum and each lateral lobe is dissected out in turn using a curved pointed scissors of the Nelson type. An incision along the medial surface of the lobe delineates that part of the epithelium which will be preserved and which will be dissected away from the benign enlargement (Fig. 2; insert A). A volsellum forceps is placed on the prostatic lobe to provide a firm hold on it and facilitate the careful scissors dissection. The epithelium is separated from the adenomatous tissue along with the thin fascial layer underlying it to ensure its viability. Firmly adherent small nodules are best left *in situ* rather than risk button-holing the epithelial flap. When both lobes have been removed in this manner, the posterior urethral wall will have been left undisturbed and the epithelial covering reflected off the lateral lobes will fall back and come to lie alongside the posterior strip (Fig. 2; insert B). Any excess tissue can be trimmed off at this stage. Postero-lateral haemostatic sutures (No. O chromic catgut) are inserted at the bladder neck which may incorporate the free lateral edges of the posterior urethral wall.

This "standard" method, just described, is applicable to the majority of cases (70%) coming to open prostatectomy in whom little or no hyperplastic tissue develops in the region of the "posterior commissure". In a proportion of patients, however, such additional benign enlargement does occur and in these cases a "variant" of the standard technique is adopted which is illustrated in Figure 3. The posterior wall of the urethra is lifted forward to permit its removal and it is then re-laid in position and fixed there by a central "boomerang" suture incorporating the bladder neck and verumontanum. A catheter is introduced at this stage.

The reconstruction, as outlined diagrammatically in the premise, is carried out by suturing the edges of the 2 bladder flaps alongside the posterior urethral wall in the following manner. A full-length No. 1 chromic catgut suture on a round-bodied No. 6 (55 mm) half-circle needle is used on each side to make a horizontal mattress stitch as shown in Figure 4. The needle is introduced from outside inwards through the capsule just below the bladder neck to emerge not far from the posterior urethral strip. It is then again passed from outside inwards through the lateral edge of the bladder flap and finally from inside outwards through the capsule posterior to the original site of entry, preferably catching the edge of the posterior urethral strip in the process. Tying of this stitch

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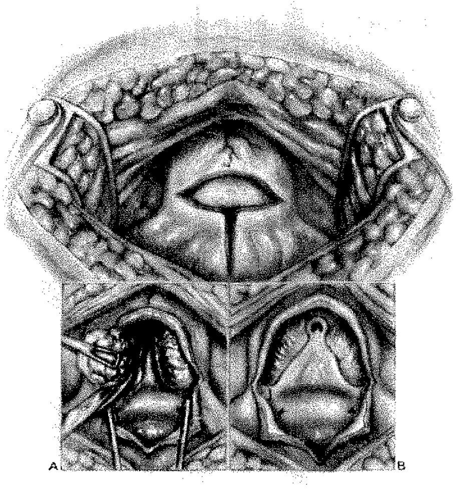

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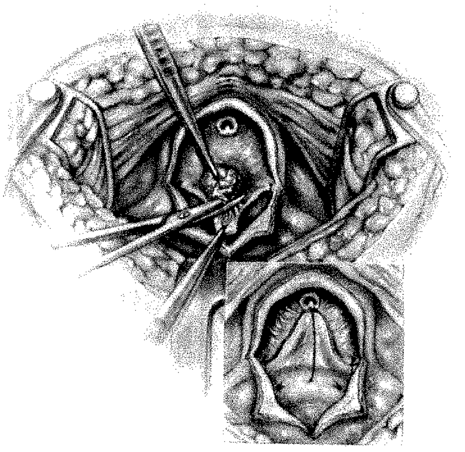

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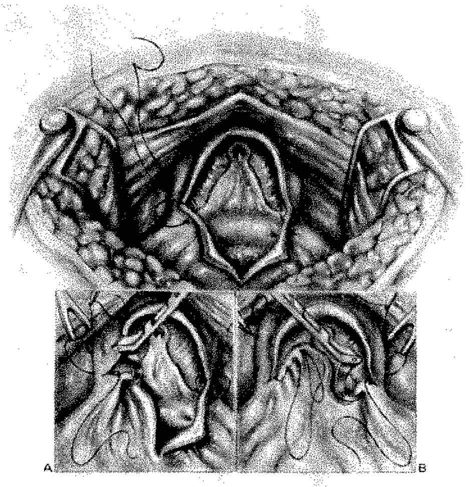

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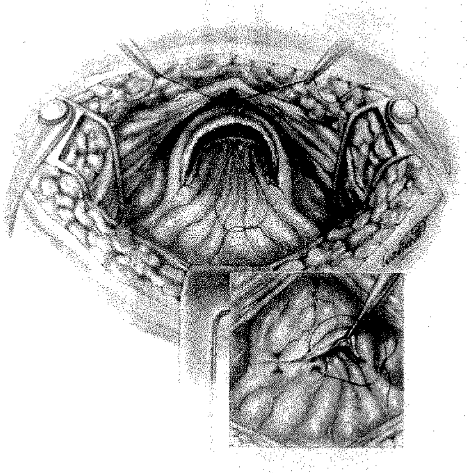

Fig. 2. Inverted T-shaped vesico-capsular incision outlining full-thickness bladder flaps. *Insert A*: scissors dissection of lateral lobes. *Insert B*: preserved posterior urethral wall and postero-lateral ligatures.

Fig. 3. Removal of benign prostatic tissue from behind posterior urethral wall and (insert) its re-application (see text).

Fig. 4. Horizontal mattress suture being inserted on left side to commence invagination of bladder flaps. *Insert A*: looping of extracapsular strand on left side and insertion of mattress stitch on right. *Insert B*: looping of extracapsular strand on right side and "chain stitch" in progress on left apposing flap to posterior urethral strip.

Fig. 5. Completion of advancement of bladder flaps and of continuous suture. *Insert*: overlap closure of prostatic capsule on bladder flaps.

commences the invagination of the flaps into the prostatic cavity, and the 2 long strands are used to execute a sewing-machine type continuous suture which will gradually advance the bladder flaps into their final position. One strand, which will come to lie outside the prostatic capsule, is looped successively through the capsule and the flaps with a boomerang needle as shown in Figure 4 (inserts A and B), while the second strand, which will come to lie "interstitially" between the outer surface of the flaps and the inner surface of the capsule, is threaded through the loops. Each loop is tightened in turn, albeit gently, first on one side, then on the other and on completion the flaps will come to be apposed alongside the preserved posterior urethral lining.

The meeting of the two halves of this suture will bring the proximal end of the vertical component of the vesico-capsular incision against the anterior edge of the partially severed urethra. The continuous watertight closure is completed by tying extracapsular strand to extracapsular strand and interstitial strand to interstitial strand.

Finally the capsule is sutured over the invaginated bladder flaps with a few interrupted No. 1 chromic stitches, using a No. 4 J-shaped needle, to complete the reconstruction of the urethra which is now virtually totally lined with transitional epithelium (Fig. 5 and insert).

The bladder is rinsed out through the catheter which may be left *in situ* for drainage or withdrawn, depending on the wishes of the operator or the merits of the individual case. The abdominal wound is sutured in layers and vacuum drainage of the pre-vesical space is provided.

Management. Since the main object of the new technique is to interpose an epithelial protective barrier into a hitherto "bare" prostatic cavity, the advantages to the patient which would devolve from it are not dependent on the absence of a urethral catheter, and postoperative management may well follow conventional lines. However, the relinquishing of the routine postoperative catheter exercised a certain aesthetic appeal and it was decided to adopt no-catheter management when the present series was embarked upon.

Experience has endorsed all the advantages claimed for no-catheter management by its originator and colleagues (Debenham and Ward, 1960; Baker, 1964) but has also led to modifications which have simplified postoperative care considerably. Most of the exclusions recommended have not been found to apply, as indicated by the consecutive nature of the series; indeed 3 cases which required simultaneous diverticulectomy voided well from the start without suprapubic leakage. The only cases that were returned to the ward with a catheter were elective cases of chronic retention.

At the end of the operation, a solution of 10% Mannitol is administered intravenously over 3 hours. The ensuing diuresis helps distinguish between those patients who would void satisfactorily and proceed to an uneventful recovery and those who would fail to achieve an anticipated output in excess of 800 ml over a period of some 18 hours from operation and would therefore require catheter drainage. This rather empirical approach has been dictated by the difficulty in palpating a distended bladder through an oedematous abdominal wall and by the unpredictability of spontaneous urine production in the immediate postoperative period. Also, patients who retain urine after operation are virtually asymptomatic in contrast to the restless, distressed and often shocked subject with clot retention following conventional retropubic prostatectomy, so that there is no reliable signal to alert the clinician to the state of overflow retention. Mannitol ensures prompt urine secretion and makes for an early decision on the need for a urethral catheter. In those cases where doubt may still exist, gentle but firm suprapubic pressure will invariably result in expression of urine in patients with impalpaply distended bladders, so providing corroborative evidence in favour of establishing drainage.

In those patients in whom catheterisation becomes necessary normal micturition would be restored in a matter of 2 or 3 days provided the detrusor is not weakened from a preceding chronic retention. Urgency and frequency of micturition is experienced soon after operation but patients usually regain adequate "control" in a few days. Mild dysuria is likewise a feature but it too abates rapidly.

Results

Table I summarises the constitution of the series and the outcome of no-catheter management. Out of 400 cases, 290 or 73% had been admitted to hospital with retention of urine, 37 of them with chronic retention. 80% of patients were in their 7th or 8th decade while a further 10% were 80 years of age or over.

Altogether 263 out of 400 cases (66%) voided without difficulty after operation. The rate for successful no-catheter management in *elective* cases is 78% and if allowance is made for 37 cases of chronic retention in which a hypotonic detrusor enforced the use of a urethral catheter, 67% of cases of *acute retention* were similarly managed without drainage.

There were 23 postoperative deaths, a rate of 5·8%. 3 deaths followed elective prostatectomy, all from pulmonary embolism. With one exception deaths following retention were equally distributed between the 8th and 9th decades, giving mortality rates in these sub-groups of 7% and 24%. The cause of death was cardiac failure in 7 patients, pulmonary infection in 7, pulmonary embolism in 3, cerebro-vascular episodes in 2, gastro intestinal haemorrhage in 1, septicaemia in 1 and oliguria and uraemia (infective) in 2.

Table I

Suprapubic Prostatectomy and Vesico-urethroplasty

Number of cases	400
Retention cases	290 (73%)
Elective cases	110 (27%)
Number in chronic retention	37
Number of cases without postoperative catheter	
Total	263 of 400 = 66%
Retention	176 of 290 = 61%
Elective	86 of 110 = 78%
Age distribution	50-59 = 35 cases
	60-69 = 176 cases
	70-79 = 151 cases
	80-89 = 38 cases
Postoperative deaths	
Total	23 (5·8%)—20 retention cases
	3 elective cases
Age distribution	60-69 = 4 cases
	70-79 = 10 cases
	80-89 = 9 cases

Table II

Suprapubic Prostatectomy and Vesico-urethroplasty
Complications—400 cases

	Operative mortality	Wound infection	Suprapubic leakage	Ascending infection	Secondary haemorrhage	Micturition disturbances	Incontinence
Prostatectomy + vesico-urethroplasty							
All cases	23 (5·8%)	76 (19%)	7 (1·7%)	9 (2·2%)	5 (1·2%)	1	0
Last 350 cases	19 (5·4%)	59 (17%)	3 (1%)	3 (1%)	5 (1·4%)	1	0
Retropubic prostatectomy							
Marshall (1967) 760 cases	45 (5·9%)	125 (16%)	50 (6·6%)	107 (14%)	34 (4·5%)	28 (3·7%)	31 (4·1%)
Magri (1975)	24 (12%)	42 (21%)	20 (10%)	23 (11%)	8 (4%)	3 (1·5%)	2 (1%)

Table II sets out the incidence of complications, allowance being made for the first 50 "experimental" cases, and includes for comparison those from the Glasgow series (Marshall, 1967) as well as those encountered in a personal series of 200 retropubic prostatectomies performed during the period immediately preceding the adoption of the new technique (Magri, 1975).

Discussion

The gradual development of prostatectomy from a blind two-stage enucleation to the more elegant "closed" modern operation has resulted in an unquestionable concurrent reduction in

Table III

Suprapubic Prostatectomy and Vesico-urethroplasty
Post operative Nocturnal Frequency

	Retropubic prostatectomy				Prostatectomy + vesico-urethroplasty
Nocturnal frequency	Caine (1954) 575 cases	Taylor *et al.* (1955) 207 cases	Barrett (1962) 405 cases	Magri (1975) 200 cases	Magri 400 cases
x 0		30·4%		46%	61%
x 1		32%	50%	28%	28%
x 2		35·6%		20%	9%
x 3	8·7%			6%	2%
x 4					
x 5		2·4%			

morbidity. Although there has been no similar reduction in mortality in representative series, which still averages between 5% and 7% (Millin, Macalister and Kelly, 1949; Salvaris, 1960; Grace, 1961; Scorer and Knight, 1962; Marshall, 1967), a notable extension in the scope of the operation evolved over the years. Our results bear out the well-documented relationship between mortality and the state of retention, advancing age and concomitant pulmonary and cardiovascular disease.

The reconstructive technique described in this paper has resulted in a significant reduction in the complication rate following prostatectomy, in keeping with the theoretical expectations (Table II). An incidence of pyelonephritis and septicaemia of 3% overall and of 1% in the last 350 cases compares very favourably with a rate of 14% (Marshall, 1967b) and 11% (Magri, 1975) associated with retropublic prostatectomy. The accuracy of the clinical assessment was verified by blood culture studies on pre-, per- and post operative samples from 108 consecutive patients. A positive blood culture was obtained in 10 patients, all of them retention cases. In 3 patients, 1 of whom had sterile urine preoperatively, bacteraemia was confirmed in the preoperative blood sample, thus invalidating the findings in later samples. In the remaining 7 patients, the organism isolated in one or more of the postoperative samples was identical with that present in the preoperative urine specimen. None of these patients showed clinical evidence of ascending infection and none had required catherisation after operation. These data, which represent an incidence of post-prostatectomy bacteraemia of 6·5%, lend support to the clinical experience and show moreover a very significant reduction in the incidence of occult blood stream infection as compared with retropubic prostatectomy. Marshall (1967) in 3 separate studies into post-prostatectomy bacteraemia spanning the 10-year period 1955 to 1964 established an average incidence of positive blood cultures in 13% of 68 patients with sterile urine and in 58% of 128 patients with infected urine. In the infected cases the incidence was 42% in 50 patients treated with antibiotics and 70% in 78 untreated patients.

The protection afforded to the patient by the vesico-urethroplasty is again reflected in the lowered percentage mortality from infective complications which has been recorded as ranging from 25% to 45% (Grace, 1961; Barrett, 1962; Scorer and Knight, 1962; Marshall, 1967). Only 3 deaths are ascribable to this cause in this series (13%) all of them occurring within the first 100 cases.

Another welcome sequel to the new technique has been the virtual abolition of the postoperative suprapubic urinary fistula, there being only 3 instances of this complication in the last 350 cases and none in the last 300. The incidence of secondary haemorrhage is also reduced, possible contributory factors being the usually undamaged postero-lateral prostatic arteries as much as the flap advancement.

The picture is equally encouraging when considering late complications. All cases have been strictly followed up for 1 year. Only 1 patient continued to attend because of persistent post-operative frequency which proved refractory to all forms of treatment, including per-urethral resection of the preserved posterior bladder neck. This patient had been shown to be voiding completely at micturating cystography prior to the resection. 2 further patients were readmitted with retention of urine due to carcinoma of the prostate and neurogenic bladder from spinal pathology respectively.

Difficulties with voiding and disturbances of continence have been conspicuous by their absence. This contrasts with the findings in our own and other series of retropubic prostatectomy (Caine, 1954; Marshall, 1967; Magri, 1975), the relevant cases in the former being 1 case of severe stress incontinence, 1 of total incontinence, and 3 of stricture. Residual postoperative noc-frequency at 1 year is also appreciably reduced (Table III).

No-catheter management allied to the new technique has proved to be simple and safe and has required the minimum of supervision. It has brought to a substantial majority of patients an unencumbered convalescence without exposing the remainder to any untoward risks. It is interesting to note that the "failure rate" of no-catheter management is not far removed from the re-catheterisation rate in conventionally managed retropubic prostatectomies, which may be of the order of 20 to 25 % in comparable series. It would seem therefore that the inability to micturate in the minority is not due directly to the absence of a catheter but is influenced by factors common to other forms of prostatectomy. Looked at in this perspective, a catheter-less prostatectomy appears even more favourable and should encourage a wider acceptance of this type of management among urologists.

Summary

A new look at the operation of suprapubic prostatectomy is suggested in view of the continuing substantial morbidity associated with traditional techniques.

The proposition is that a reconstructive as distinct from a simple ablative operation is possible, notwithstanding long-standing beliefs to the contrary. The writer goes on to outline the principles, and to describe and illustrate in detail the steps in a new technique of prostatectomy combined with a urethroplasty, which uses full-thickness bladder wall flaps to provide immediate epithelial cover for the denuded surfaces of the prostatic urethra.

The theoretical advantages of such a technique are borne out by the results in the first 400 cases so treated, which are contrasted with those from a comparable personal series of 200 retropubic prostatectomies and other representative series.

I am deeply indebted to Miss F. Wadsworth for the drawings.

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Urinary Tract Infection following Trans-rectal Biopsy of the Prostate

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Trans-rectal prostatic biopsy has been used for some years as a method of obtaining tissue for histology and reported complications of the procedure are uncommon. Wendel and Evans (1967) in a review of over 4,300 cases of punch biopsy of the prostate by both trans-rectal and trans-perineal routes found an overall incidence of complications of 3·7% with one case of "pyelonephritis". In their own series of 250 cases the incidence was 7·2% with one case of "cystitis". In a later study, Davison and Malament (1971) found that of 50 patients with negative urine cultures before trans-rectal biopsy 17·7% developed a urinary tract infection following the procedure, on one occasion associated with a fatal septicaemia with *E. coli.* This paper compares the incidence of urinary infection following trans-rectal biopsy with that following simple endoscopy.

Patients and Methods

All trans-rectal biopsies in this department are preceded by bladder endoscopy which in itself carries a risk of urinary infection. Two surveys were therefore undertaken:

1. A retrospective survey of all cases of trans-rectal biopsy of the prostate performed between 1968 and 1973 for whom detailed records of pre- and postoperative urine cultures and antibiotic therapy were available. Urine was considered infected if a mid-stream specimen contained 10^5 or more bacteria per ml.
2. A prospective survey of urinary tract infection following bladder endoscopy to establish the incidence of urinary infection attributable solely to the biopsy procedure. We studied male patients who were having simple diagnostic urethral and bladder endoscopy under general anaesthesia either as in-patients or out-patients. Preoperative urine specimens were collected after the passage of the cystoscope and postoperative cultures were obtained on the fourth day following the procedure using the 'Dipinoc' type of dip inoculum which was sent to the Microbiology Department.

In both groups of patients the urine was known to be sterile at the time of the biopsy. Any patient with infected urine at the time was automatically excluded from the study, and any patient for whom the bacteriological state of the preoperative urine was not known was also excluded.

Results

1. Retrospective survey: a total of 56 trans-rectal biopsies had been performed but in only 44 were sufficient bacteriological data available for analysis. Of these 44 cases, 17 had received antibiotic therapy which had begun the day *after* the procedure.

Table I shows the incidence of urinary tract infection and the organisms isolated in these patients.

2. Prospective survey: a total of 137 cystoscopies were performed but 14 of the patients failed to return the dipslides to the laboratory. The incidence of infection for the 123 patients whose dipslides were returned and the organisms cultured from their urine are shown in Table II.

Table I

Incidence of Urinary Tract Infection following Trans-rectal Biopsy

	No. patients	Infected post-op.	Uninfected post-op.
No systemic antibiotics	27	12 (44·5%)	15 (55·5%)
Systemic antibiotics	17	5 (30·0%)	12 (70·0%)
Total	44	17 (38·5%)	27 (61·5%)

Organisms isolated: E. coli, 10 (2 positive blood cultures); S. faecalis, 5; E. coli+S. faecalis, 1; P. mirabilis, 1.

Table II

Incidence of Urinary Tract Infection following Cystoscopy

No. patients	Post-op infection
123	9 (7·6%)

Organisms isolated: E. coli, 6; S. faecalis, 2; Klebsiella, 1.

Discussion

Our retrospective survey of patients undergoing trans-rectal biopsy of the prostate showed that 38·5% of the 44 patients developed urinary tract infection, on at least 2 occasions with accompanying bacteraemia. This rate is twice that quoted by Davis and Malament (1971) and is unacceptably high. The postoperative "prophylactic" systemic antibiotics which 17 of the patients received reduced their infection rate to 30% compared with an incidence of 44·5% in the 27 patients who did not receive antibiotics. A course of "prophylactic" systemic antibiotics given *after* the operation would seem to have achieved only a minor reduction in the infection rate (from 44·5% to 30%). It is possible that if an adequate concentration of a suitable antimicrobial had been present in both blood and urine at the time of the trans-rectal biopsy the results might have been different.

Since in all the patients undergoing prostatic biopsy the procedure was preceded by endoscopy the object of the prospective survey was to assess how often urinary infection was likely to occur from this alone. The incidence of 7·6% was considerably lower than that following prostatic biopsy though the bacteria isolated were similar. We conclude that trans-rectal prostatic biopsy results in an increased incidence of postoperative urinary infection. It seems likely that this arises either from perforation of the bladder base or direct implantation of faecal bacteria into the prostatic ducts.

It might be possible to prevent such infections by administering a systemic antibiotic *before* the procedure thereby ensuring maximum blood and urine concentrations of the drug at the time of the biopsy.

Summary

An unacceptably high incidence of urinary tract infection was found in a retrospective survey of patients undergoing trans-rectal biopsy of the prostate.

The incidence was considerably greater than that found in a prospective survey of bladder endoscopy alone.

It is suggested that preoperative antibiotic prophylaxis might be worthwhile in this situation.

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Short Case Report

A Case of Bilateral Cystadenoma of the Epididymides presenting as Infertility

Case Report

A 32-year-old man presented in March 1973 complaining of infertility. Physical examination was normal apart from the epididymides. The upper pole of each was enlarged (3 cm × 1½ cm), hard, irregular and non-tender. The sperm count was 20,000/ml.

Exploration of the right scrotum was performed in May 1974. The enlarged upper pole of the epididymis and the testis were biopsied. Vasogram was normal.

Histology of the epididymis showed the appearances of a cystadenoma of the epididymis (Fig.) (Sherrick, 1956).

Although the left side was not explored the clinical findings were identical to those on the right side.

Comment

This rare epididymal tumour usually presents as a scrotal swelling or is found on routine physical examinations. It is benign and treatment conservative.

Its main importance is that it may be a feature of a systemic disorder known as Lindau's disease (Melmon and Rosen, 1964). In this disease, haemangioma(s) of the central nervous system are associated with various visceral cystic and epithelial tumours, (including epididymal papillary cystadenoma, pancreatic and renal cysts and hypernephromas). Lindau's disease is inherited as an autosomal Mendelian dominant.

Lindau's disease should, therefore, be excluded in patients with this epididymal tumour (Price, 1971). A family history of central nervous system tumours is suggestive. Physical examination should include examination of the fundi to exclude retinal haemangioma and an intravenous urogram should be part of the investigations.

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We would like to thank Mr N. A. Green for his help and permission to report this case.

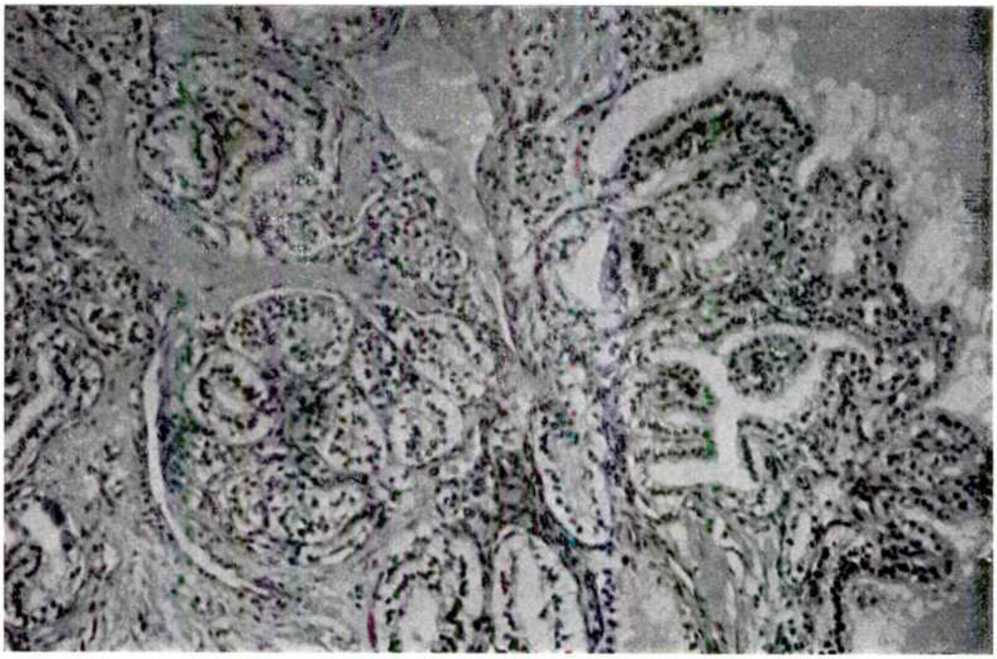

Figure. Intraductal papillary proliferation of epidymal ducts. H & E. × 90.

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Iglesias Resectoscope with Continuous Irrigation, Suction and Low Intravesical Pressure

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This resectoscope has been designed to avoid the present inconvenience of periodically interrupting the resection in order to evacuate the accumulation of blood-stained fluid from the bladder, at the same time maintaining the intravesical pressure constantly below 10 mm Hg. Using isotopes in 1973, Madsen established 30 mm Hg as the initial intravesical pressure for irrigant absorption during transurethral resection of the prostate, but we have found the intravesical hydrostatic pressure should be under 10 mm Hg to avoid the absorption of electrolyte-free irrigant.

The new resectoscope has 2 conduits, one for the inflow of clear fluid and the other for the outflow of blood-stained fluid. Both are completely separate and have their distal openings located at different sites in the beak of the resectoscope sheath. The volumetric capacity of the outflow conduit is smaller than the inflow conduit. In order to avoid overdistension of the bladder, suction is applied to the outflow to establish an equal rate of flow in both conduits. Clear fluid is constantly flowing in front of the lens. The inflowing fluid irrigates the operative field before being evacuated via the outflow conduit. The bladder and prostatic urethra must be moderately distended to allow exact visualisation of the pathological changes in the prostatic urethra. At 10 mm Hg pressure, bleeding is decreased allowing uninterrupted resection. To maintain the bladder and prostatic cavity adequately distended at all times with an inflow of over 600 cc per fluid minute, with irrigant at any height above 70 cm it is necessary to regulate the suction pump. We have learned in our research while measuring the intravesical pressure that the bladder can be adequately distended, at pressures less than 10 mm Hg or 13·6 cm water. At these levels of pressure, the resectionist is able to see the posterior wall of the bladder while the resectoscope is in the prostatic fossa.

The outlet channel is provided by a fine concentric metallic inner tube throughout the entire length of the sheath. The inflow conduit is within the inner metallic tube as the free space surrounding the telescope, loop, stem and arms. At the beak, the pressure of the inflowing irrigant pushes the resected pieces of tissue to the bottom of the bladder. Blood-stained irrigant from the bladder enters the outflow conduit by way of multiple holes around the distal part of the sheath preventing resected pieces from blocking the outflow entrance. At the upper proximal end of the sheath socket, the inflow conduit communicates with an external tube connection through which clear irrigating fluid flows to the operative field. The outflow conduit communicates at the lower part of the socket with an external tube to which suction is applied as seen in Figures 1 and 2.

Both external tubes are supplied with stop-cocks. Just proximal to the outflow stop-cock there is a filter device which prevents the suction tube from becoming plugged. A metal tube on the cutting loop stabilises the loop and also deflects the arms of the loop upward and out of the field of vision.

By operative monitoring of intravesical hydrostatic pressure and observation of serum chemistry, pre- and postoperative weights, and volume of irrigants used, we have found that there is a minimal absorption of irrigant at an intravesical pressure under 10 mm Hg. A typical patient record is seen in Table I. Above this critical pressure, absorption of irrigant rapidly increases.

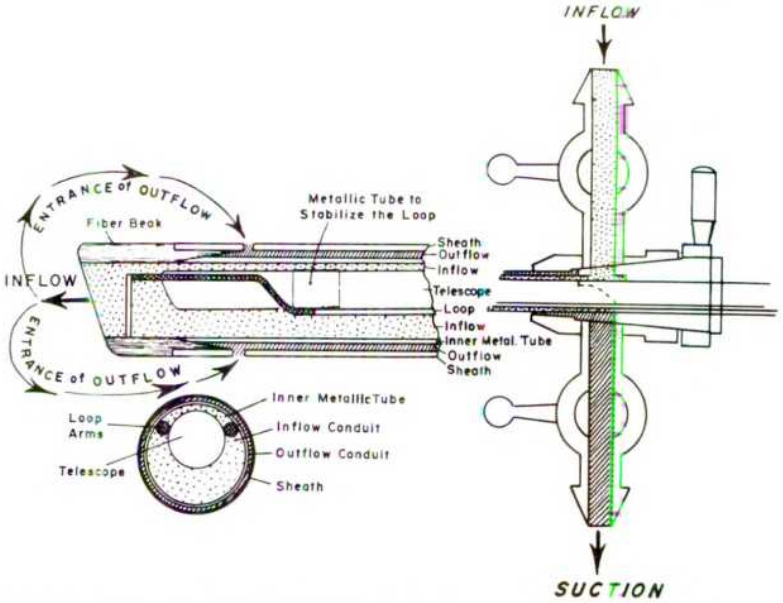

Fig. 1. Iglesias resectoscope with continuous irrigation, suction and low intravesical pressure.

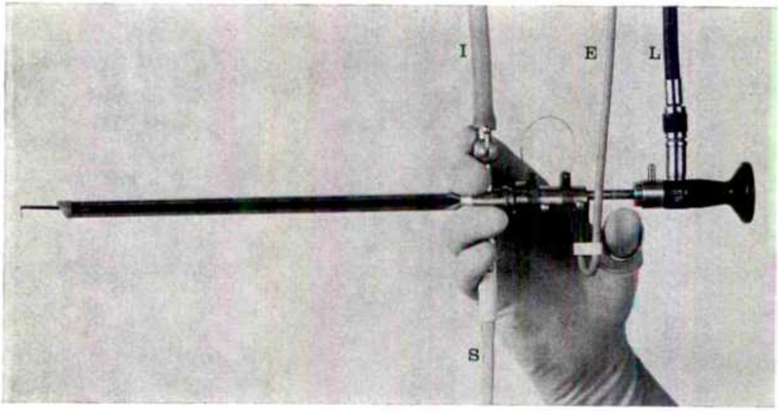

Fig. 2.
I—Irrigation tube;
E—High-frequency electrical current;
L—Light bundle cord;
S—Suction tube.

During our research with the new resectoscope, a fine suprapubic catheter connected to a Lewis cystometer or to a water manometer allowed continuous monitoring of the intravesical pressure which was maintained below the critical 10 mm of Hg. A typical tracing is seen using the conventional resectoscope and the new suction resectoscope in Figures 3 a and b.

The handling of this resectoscope is very simple. The irrigating flask should be at 70 cm or more above the level of the operating table. Suction is applied to the outflow conduit only after the posterior wall of the bladder is completely separated from the bladder neck while the bladder is filling, and then is regulated by the pump to maintain the posterior bladder wall away from the bladder neck, at any intravesical pressure below 10 mm Hg. Regulation of the suction eliminates the danger of having to elevate the irrigant containers. Maximum visibility and minimal bleeding are realised with undisturbed haemodynamics and undetectable irrigant absorption if the periprostatic sinuses are not opened. The performance, teaching, still photography and endoscopic

Table I

Typical Protocol Form demonstrating Pre- and Postoperative Findings while using the Iglesias Resectoscope with Continuous Irrigation, Suction and Low Intravesical Pressure

Name	A. G.	Operative Time	35 min
Age:	64 years	Adenoma weight	45 g
Diagnosis:	B.P.H.	Irrigant used:	24 H_2Ol
		Blood-stained fluid sucked	23·5 l

	Pre-op	Post-op
Blood pressure	149/90	135/90
Serum osmolality	289 mOS	287 mOs
Weight	145 lb	145 lb
Serum-free haemoglobin	2·4 mg%	2·3 mg%
Serum sodium	138 mEq%	142 mEq%
Serum chloride	104 mEq%	102 mEq%
Serum potassium	3·2 mEq%	3·2mEq%
Haematocrit	39%	40%

cine during transurethral surgery is made easier. The operator can appreciate the amount of bleeding through the transparent suction tube.

Explosive gases produced during the resection are removed from the bladder thus avoiding possible explosion which has been reported with the use of suprapubic trocar suction. The vacuum pump must be adjustable between 10 and 50 cm Hg Vacuum. The loop must be adjusted to the correct position prior to beginning surgery *so that it is situated just inside the sheath while viewing through* the telescope. *When evacuating pieces of tissue from the bladder the outflow stop-cock must be closed to ensure it will not become blocked.*

The resectoscope (manufactured by Karl Storz K G, W. Germany) has two sheaths; the 25 Fr. accommodates a yellow loop 26 and the sheath 28 Fr. uses a black loop larger than the blue 28. The 25 Fr. sheath can be used for most cases.

Summary

A resectoscope with continuous irrigation, suction and low intravesical pressure is described.

Advantages of this instrument include: no interruption, better endoscopic vision by a continuous clear inflow of more than 600 ml per min, a constant intravesical pressure less than 10

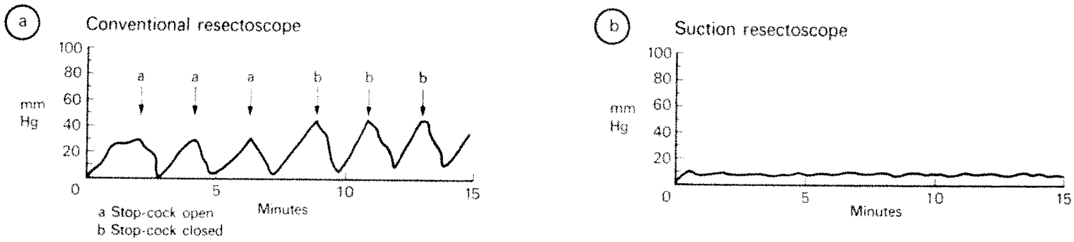

Fig. 3. Continuous intravesical pressure recording by Lewis cystometer via suprapubic cystocath during TUR's using (*a*) the conventional resectoscope and (*b*) the suction resectoscope.

mm Hg during the resection, shorter operating time, less bleeding, easier teaching and no more wet floor and wet surgeon.

Since the entire amount of irrigating fluid is collected, blood loss can be calculated and the amount of absorption determined.

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Cysts of the Prostate

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Cysts of the prostate are a rare clinical entity and few cases have been reported in the literature. The aim of this paper is to present 2 such cases which have been treated in our department.

Case Reports

Case 1. A male patient aged 31, married and the father of one, was hospitalised in our department because of frequency, nocturia and rectal fullness of 4 years' duration.

Rectal examination revealed a large, round cystic swelling measuring 5 cm in diameter located in the middle line in the region of the prostate. Further physical examination showed no abnormality. Routine laboratory tests, including haemogram, ESR, blood urea nitrogen (BUN), urine analysis and culture, were all within normal limits.

Intravenous pyelography (IVP) showed no abnormality. Under general anaesthesia the cystic swelling was aspirated transrectally and 65 cm of clear fluid were obtained. The fluid contained no sperms. It was sterile on culture. The cavity was then filled with contrast medium (Fig. 1). The A-P X-ray showed a round cyst with a diameter of about 5 cm as well as a convoluted formation, which was most probably the left seminal vesicle. On a lateral film (Fig. 2), the cyst proved to be anterior to the seminal vesicle.

Following aspiration of the cyst, pain and high fever developed. There was a good response to antibiotics and he was discharged 1 week later in good general condition. 4 days later he was readmitted because of right epididymo-orchitis. Rectal examination at the time revealed no abnormality. Antibiotics were resumed and the epididymo-orchitis subsided. Prolonged follow-up showed him to be feeling well, with rectal examination showing no recurrence of the cystic swelling.

Case 2. A 60-year-old patient was hospitalised because of dysuria and dribbling of urine. Rectal examination revealed an enlarged prostate which was obviously cystic in consistency. Routine laboratory tests, including

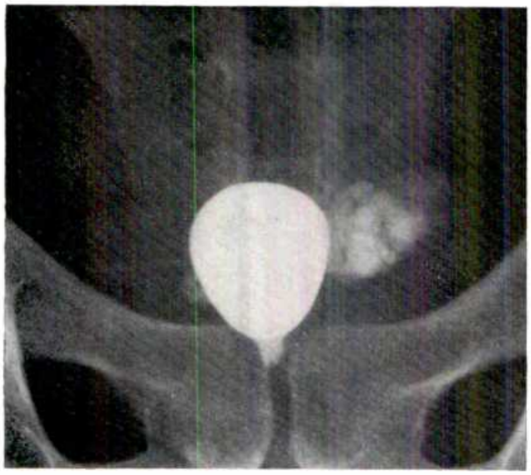

Fig. 1. Case 1: Transperineal injection of contrast medium into the emptied cyst. A-P X-ray shows a round, midline cyst and also visualises the left seminal vesicle.

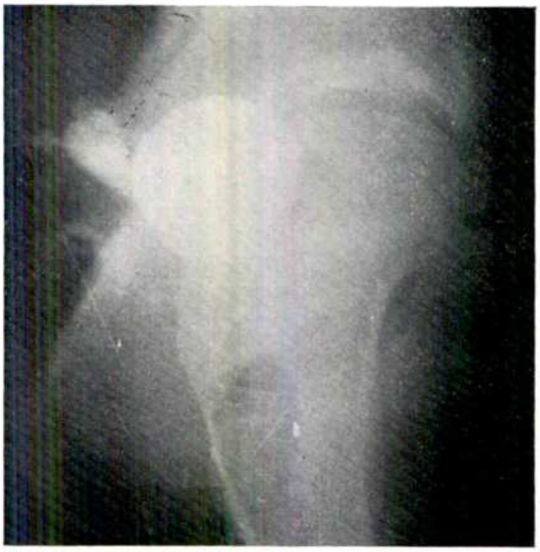

Fig. 2. Case 1: A lateral view of the cyst showing that it lies anterior to the seminal vesicle.

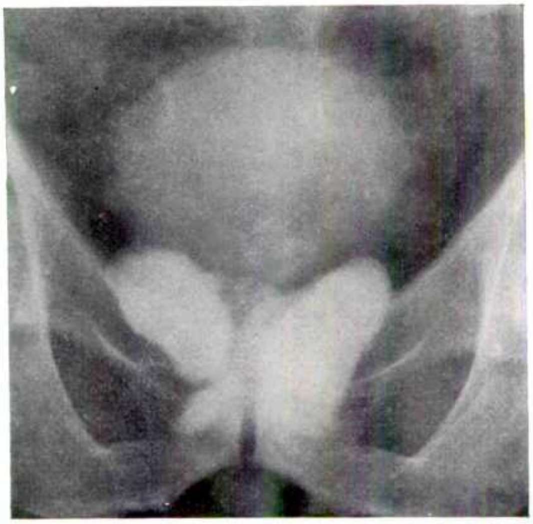

Fig. 3. Case 2: A-P X-ray after perineal aspiration of the cystic prostate and injection of contrast medium, demonstrating the large cysts in the lateral lobes of the prostate.

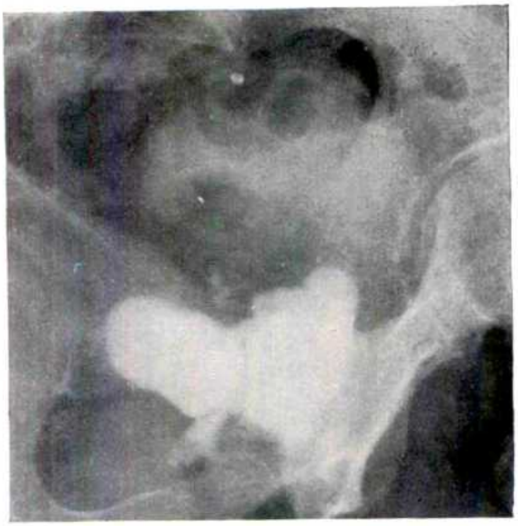

Fig. 4. Case 2: Lateral view of the prostatic cysts.

haemogram, blood sugar, BUN, urine sediment and culture, were all within normal limits. IVP showed a normal upper urinary tract. An enlarged prostate was visualised as causing an impression at the base of the bladder. Under general anaesthesia the cystic prostate was aspirated perineally and 150 cc of clear fluid were obtained. The contrast material which was then injected filled two formations at the base of the bladder: the two lateral lobes of the prostate (Figs. 3 and 4).

Following this procedure there was an alleviation of the patient's symptoms and he was discharged 5 days later. 1 month afterwards he was readmitted because of recurrence of his symptoms. A retropubic prostatectomy was performed with some difficulty: there was no clear plane of cleavage, the adenoma having to be removed piecemeal. During the dissection the fluid escaped from the cysts. The postoperative course was uneventful. Follow-up has shown that the patient is well, with no further complaints.

Discussion

There is considerable controversy in the classification of cysts of the prostate. Wesson (1925), who was the first to study the subject of cysts in the region of the urethra, distinguished between cysts of the urethra proper and cysts of the prostate gland and suggested a classification of prostatic cysts which is still accepted today, with minor modifications.

Magri (1960) classifies cysts of the prostate as congenital and acquired. The congenital cysts arise from remnants of the Wolffian and Müllerian duct systems. The acquired cysts are further subdivided into the following (1): parasitic cysts, which have been described in bilharzia and in hydatid disease; (2) cysts associated with carcinoma of the prostate; and (3) retention cysts, which are simple dilatations of the acini of the prostate caused by obstruction of their ducts.

The above classification does not appear to be accurate. The congenital Müllerian duct cyst does not occur within the prostatic gland but lies outside the prostate between the bladder and rectum and always in the midline. As for acquired cysts, it would seem that the retention cysts are the true cysts of the prostate, whereas the entity of parasitic cysts is open to discussion. Hydatid cysts lie close to but outside, the bladder and prostate. There is only one report of bilharzial ova seen in the wall of a cyst of the prostate and this may have been merely a coincidence (Emmett and Braasch, 1936). Cysts associated with carcinoma of the prostate may be due to cystic degeneration of a carcinoma of the prostate or the development of a carcinoma in the wall of an already present cyst.

Small cysts of the prostate gland are frequently observed at necropsy. Rarely does a cyst attain a diameter of 1 cm or more in size (Rieser and Griffin, 1964). In case 2 described above, each of the 2 lateral lobes of the prostate contained quite a large cyst. We consider that this is a very rare case of true prostatic cyst. The cyst in case 1 can be considered as originating from the Müllerian duct system since it was located in the midline, as is usually true of these cysts. The only point which is not clear is the filling of the left seminal vesicle which was seen in the X-ray performed after aspiration of the cyst and injection of the contrast medium.

Summary

2 rare cases of prostatic cysts are described. The first was considered to be a congenital cyst originating in the Müllerian system and the second a large retention cyst of the prostate.

The problems arising from the present classification of prostatic cysts are briefly noted.

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Short Case Report

Penile Amoebiasis: an Unusual Presentation

A 65-year-old widower had dysuria, multiple ulcers and pain at the glans penis for 3 months. He had phimosis and around the coronal region there was tenderness and induration. Circumcision was done after a course of antibiotic therapy. Macroscopically the excised penile skin had raised umbilicated greyish white lesions, pin-point to 0·5 cm diameter. Cut surface showed tiny ulcers with a yellowish necrotic base. Microscopically there were large numbers of amoebae in the superficial part of the ulcer, with dense monocytic exudate in the deeper areas (Fig. 1). There was attempted regeneration of ulcerated epithelium. The patient responded well to the metronidazole therapy.

Comment

Penile amoebiasis, an extremely rare condition, is either the result of aberrant sexual habit or an extension of perineal ulceration caused by amoebic proctitis. It can also occur as a venereal infection, when the mate is suffering from amoebic cervicitis and vaginitis, as recorded by Mylius and Tenseldam (1962). Subramaniam (1968) also mentioned the rarity of penile lesions in cutaneous amoebiasis. In view of the extreme rarity we wish to record the present case and suggest that penile amoebiasis should be considered in the differential diagnosis of ulcerative lesions of glans penis especially in countries where amoebiasis is common.

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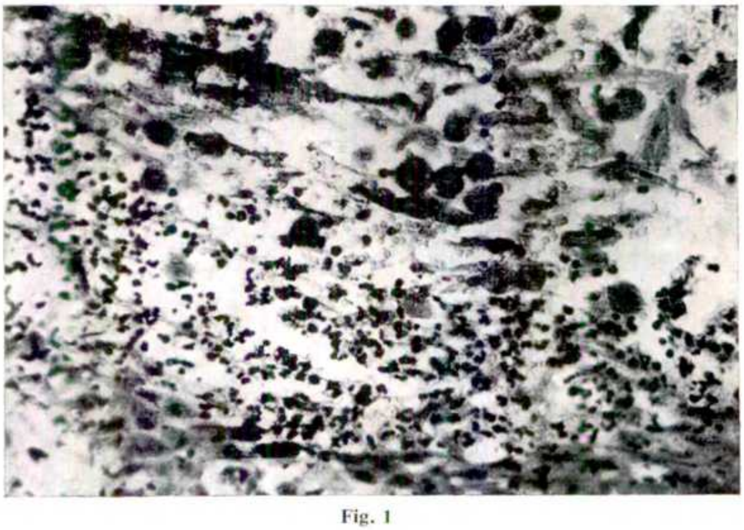

Fig. 1

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Urinary Pathogens in the Male

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It is accepted that, in the vast majority of cases, the route of infection in the urinary tract is ascending, and there is considerable evidence that in the female the infecting organisms originate in the bowel (Grüneberg, 1969). There is, as yet, insufficient understanding of the factors which determine the ability of a particular organism to establish itself in the urinary tract; in the case of *Escherichia coli*, the commonest urinary pathogen, it seems likely that the antigenic character of the organism and host factors each play a part. Much attention has been paid to the elucidation of this problem in the female, but the pathogenicity of bacteria in the male urinary tract has been studied less.

In 1971-72 we noticed the frequency of Proteus species as the infecting organisms in urinary infection in boys, in marked contrast to the predominance of *Escherichia coli* in girls. The incidence of *Proteus* infection in boys was also noticed by Bergström (1972) and Mann (1972).

We report some bacteriological data which suggest a possible explanation of this phenomenon.

Methods

The mid-stream urine (M.S.U.) specimens from children aged 1 to 12 years were cultured on cysteine lactose electrolyte deficient (CLED) agar at the request of their general practitioners for diagnostic, not screening, purposes. The laboratory provides instruction sheets, good collection and refrigeration facilities and dip-inoculation spoons (Mackey and Sandys, 1965) for use by patients at a distance. The quality of specimens received is good. The M.S.U.s from adult males with symptomatic urinary infection were received from practitioners and from hospital out-patient departments. 10^5 organisms/ml in pure culture was accepted as the criterion of urinary infection.

Swabs from the preputial sac (meatal area in circumcised boys) and from the perineal area were taken from 49 boys aged 2 to 12 years known to have had proven urinary infection, by a nurse in a hospital clinic. At the time the swabs were taken the urinary infection had been successfully treated. Preputial swabs were also taken from 51 boys in a control group by a nurse in a general practitioner's surgery. The boys in the control group were carefully matched for age and social class, had no history of urinary symptoms or evidence of urinary infection in the past, and had not received antibiotics within the previous week. None of the boys in either group had any evidence of balanitis; 4 boys in each group had been circumcised.

Results

From May 1974 to February 1975 inclusive, 52 episodes of urinary infection were diagnosed in 46 boys. Table I compares the infecting organisms with those in 223 episodes of infection in 191 girls during the same period. The difference in the relative number of *Proteus* to *E. coli* and coliform infections in the 2 sexes is highly significant. ($\chi^2 = 55{\cdot}2$ $P = <0{\cdot}001$) (Table I).

In addition, 43 M.S.U.s from 34 boys, and 48 M.S.U.s from 40 girls yielded a pure culture of 10^4 organisms/ml (Table II.)

Table III compares the organisms isolated from the preputial swabs of the boys in the urinary infection and control groups.

Table IV shows the organisms isolated from the perineal swabs of the boys in the urinary infection group. *Proteus* was isolated from only 1 boy.

In the light of these observations, an analysis was made of the organisms causing symptomatic urinary infection in adult males during 16 weeks from 1st December 1974. No postoperative or instrumented patients were included. Table V shows the infecting organisms. The difference in the relative incidence of *Proteus* and *E. coli* and coliform infections in the men under and over 60 years of age is significant. ($\chi^2 = 8{\cdot}5$ $P = <0{\cdot}01$). The difference between the boys of 1 to 12 years, and the men of 14 to 60 years is highly significant. ($\chi^2 = 21{\cdot}65$ $P = <0{\cdot}001$).

Table I

Organisms Causing Urinary Infection in Boys and Girls aged 1 to 12 Years inclusive. May 1974 to February 1975

	Boys		Girls	
Organism	No.	%	No.	%
Esch. coli and other coliforms	27	52	198	89
Proteus spp.	23	44	11	5
Coagulase negative staphylococci	2	4	7	6
Staphylococcus aureus	0		1	
Streptococcus faecalis	0		4	
Other streptococci	0		2	
Total	52	100	223	100

Table II

Organisms Isolated in Pure Culture of 10^4/ml in Boys and Girls

	Boys		Girls	
Organism	No.	%	No.	%
Esch. coli and other coliforms	11	25	38	80
Proteus spp.	27	63	4	8
Pseudomonas spp.	0	12	2	12
Streptococcus faecalis	5		3	
Staphylococcus aureus	0		1	
Total	43	100	48	100

Discussion

Some preliminary conclusions can be drawn from these findings. It is well recognised that the organisms causing urinary infection in females are derived from the bowel and the proximity of the short urethra to the anal area facilitates ascending infection. The finding that swabs from the perineal area of boys known to have had urinary infection rarely yielded Gram-negative organisms suggests that the focus of infection in males is elsewhere. Swabs from the preputial sac yielded

Table III

Comparison of Preputial Flora in 49 Boys in the Urinary Infection Group and 51 Controls

	Urinary Infection Group 49 boys		Controls 51 boys	
Organisms	2-5 yrs	6-12 yrs	2-5 yrs	6-12 yrs
Gram-negative organisms in pure culture	0	4*	0	0
Mixed culture including Gram-negative organisms	10	11	5	0
Gram-positive organisms	11	12	11	17
No growth	0	1	3	15
Total	21	28	19	32

* *Proteus* 3. *Pseudomonas* 1.

Table IV

Organisms Isolated from Perineal Swabs from 49 Boys in the Urinary Infection Group.

Organism	No.	%
Mixed culture including Gram-negative organisms*	8	16
Gram-positive organisms	33	68
No growth	8	16
Total	49	100

* *Proteus* 1. *E. coli* and coliform 7.

Table V

Organisms Isolated from 95 Adult Males with Symptomatic Urinary Infection. December 1974 to March 1975

	14-60 yrs		>60 yrs	
Organism	No.	%	No.	%
Esch. coli and other coliforms	63	88	12	52
Proteus spp.	5	7	7	30
Pseudomonas spp.	0	5	1	18
Coagulase-negative staphylococci	3		0	
Streptococcus faecalis	1		1	
Other streptococci	0		2	
Total	72	100	23	100

Gram-negative organisms in 25 (51%) of the boys who had had urinary infection, *Proteus* predominating over other organisms in a ratio of nearly 2 : 1. These boys were distributed over the whole age range. In marked contrast, Gram-negative organisms were isolated from the preputial swabs of only 5 boys (10%) in the control group and all were under 6 years of age. It seems, therefore, that Gram-negative organisms are established in the preputial sac of only a small minority of boys and that they tend to disappear after the age of 5, presumably as a result of better hygiene and full retractability of the foreskin. They may, however, persist in some boys and provide a focus of ascending infection. A pure culture of 10^4 organisms/ml was found in 43 M.S.U.s from 34 boys aged 1 to 12 years with symptoms of urinary infection (Table II). This observation and the finding that the preputial swabs yielded pure cultures in only 4 boys in the urinary infection group (Table III) suggests that these organisms may reside in the urethra or prostatic ducts. *Proteus* species predominated markedly over other Gram-negative organisms in the 10^4 cultures from boys, and also caused a significantly greater proportion of symptomatic infections in boys than in girls or in adult males below the age of 60 years.

This evidence, therefore, suggests that *Proteus* can become established in the urethra or preputial sac of pre-pubertal males, and that, at puberty, the situation alters. After the age of 60 years the proportion of *Proteus* infections appears to increase again. It seems possible that this phenomenon is related to prostatic secretion (Stamey *et al.*, 1968) and it merits further study.

Summary

Evidence is presented that the pathogens causing urinary infection in boys differ significantly from those causing infection in girls and in adult males. Studies of the prepuce flora in boys known to have had urinary infection and in matched controls suggest that the focus of infection is in the preputial sac or urethra, rather than the bowel as in girls. It is suggested that the difference in infecting organisms in boys and in adult males may be related to prostatic secretion.

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Volume Estimation of the Seminal Vesicles by Means of Transrectal Ultrasonotomography: A Preliminary Report

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To date, the only clinical method of seminal vesiculography has been by vasopuncture (Belfield, 1913; Vestby, 1958). Vasopuncture, however, may incidentally result in stenosis of the vas later. It should thus not be used for investigation of those patients who hope subsequently to achieve fertilisation.

A new method which can provide details of the seminal vesicles as well as other intrapelvic organs without any complications has therefore been developed. It is referred to hereafter as transrectal ultrasonotomography (Watanabe *et al.*, 1971; Tanahashi *et al.*, 1974*a*; Watanabe *et al.*, 1975).

In this preliminary report, volume estimation of the seminal vesicles, which is one of various diagnostic applications of the method, is discussed.

Materials and Methods

Special equipment for transrectal ultrasonotomography in the sitting position, developed in our laboratory, was used for the study (Watanabe *et al.*, 1974*a*; Tanahashi *et al.*, 1975).

The equipment consists of 3 parts: a transrectal transducer assembly, a radial scanner and a chair (Fig. 1).

The transrectal transducer assembly consists of a double tube system; a concave barium titanate oscillating disc is placed in the top of the rotative inner tube of the transducer assembly. The oscillating disc is 10 mm in diameter and 60 mm in radius of curvature and its resonant frequencies is 3·5 MHz. The top part of the assembly is covered with a polyethylene tube 12 mm in diameter and 0·5 mm in thickness for the protection of rectal wall from

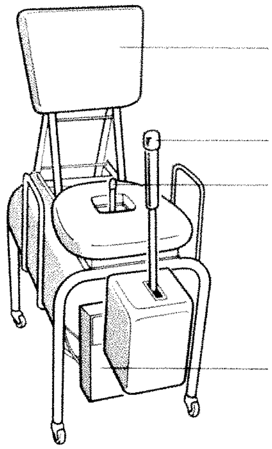

Fig. 1. Special equipment for transrectal radial scanning.

(a) Backrest

(b) Direction adjustment lever

(c) Transrectal probe (transducer assembly)

(d) Scanner.

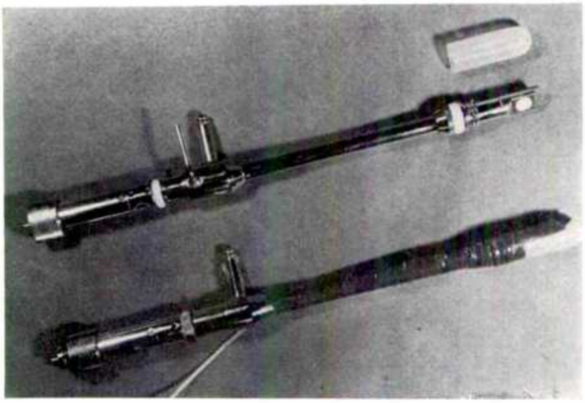

Fig. 2. Transrectal radial scanning transducer assembly. Polyethylene tube is removed in the top probe.

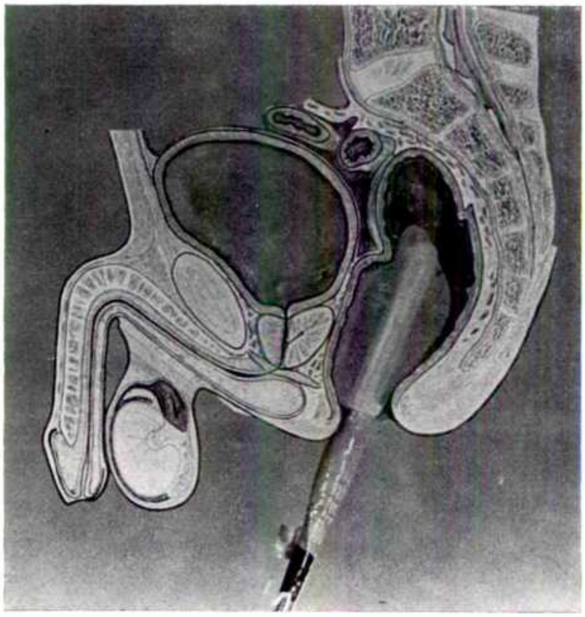

Fig. 3. Transrectal probe in use. After insertion into the rectum, the latex balloon is filled with 30-50 ml of simple tap water.

injury when the radial scanning is being performed. The outer diameter of the transrectal probe is therefore only 12 mm (Fig. 2). This tube is also wrapped in a thin latex balloon which should be filled with water after insertion. The surface of the balloon is coated with lubricant jelly for good coupling between rectal wall and latex balloon.

The chair has a hole, over which the anus is positioned and the probe is introduced into the rectum from below. The direction of insertion of the probe can be changed freely with a direction adjustment lever.

After insertion of the probe into the rectum through the anus, the latex balloon is filled with 30 to 50 ml of simple tap water until the transducer remains airtight against the rectal wall (Fig. 3).

The pulse repetition rate is 1,000 per sec. The echoes are received by the same transducer and are displayed on a cathode ray oscilloscope by the technique of brightness modulation. A potentiometer is used to show the direction of the ultrasonic beam on the cathode ray oscilloscope in accordance with the rotatory angle of the transducer. An anatomical picture of the area scanned is thus built up—radial B scanning (Fig. 4). The echographic pattern is photographed with 35 mm camera.

In our laboratory, transrectal ultrasonotomography of the seminal vesicles as well as the prostate and the urinary bladder have been performed on over 500 cases to date. The volume estimation of the seminal vesicles and prostate was made on 27 selected cases. These included 7 normal subjects, 7 cases of benign prostatic hypertrophy, 8 cases of prostatic cancer and 5 cases of Klinefelter's syndrome. The examination was performed prior to treatment in all cases.

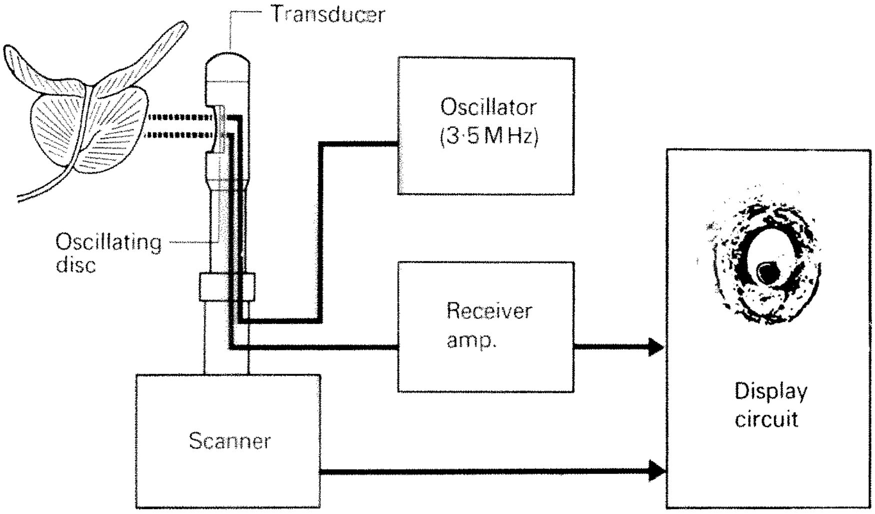

Fig. 4. Whole system of transrectal radial scanning.

In order to take readings, the scanner was inserted 8 to 10 cm; as it was lowered, horizontal sections were taken at 5 mm intervals until the anus was reached. The depth from the anus at which the seminal vesicles and the prostate appeared and disappeared on the tomogram was noted.

The volume of the seminal vesicles and the prostate were estimated from the sum of the areas of horizontal sections represented on several ultrasonotomograms (the "pile method"). The range of error in the measurement of prostatic size using sections 5 mm apart has been previously shown to be less than 5% (Watanabe *et al.*, 1974*b*). It was presumed that the same margin of error would be found in the measurement of the seminal vesicles.

Results

Normal subjects: In the 7 normal subjects, the seminal vesicles were shown on the horizontal sections taken at an average depth of from 8·0 to 4·0 cm from the anus. The seminal vesicles were shown on the tomogram as two symmetrical spindle shapes (Fig. 5). The estimated volumes of the seminal vesicles were from 8·0 to 18·6 ml and of the prostates were from 13·2 to 26·9 ml.

Prostatic Hypertrophy. In the 7 cases of prostatic hypertrophy the seminal vesicles appeared at an average depth of from 6·0 to 3·5 cm from the anus. They were shown on the tomogram in most cases as 2 symmetrical spindle-like shapes (Fig. 6). The estimated volumes of the seminal vesicles were from 5·1 to 15·9 ml and of the prostrates were from 24·0 to 81·2 ml.

Prostatic Cancer. In the 8 cases of prostatic cancer the seminal vesicles appeared at an average depth of from 7·0 to 4·0 cm from the anus. The tomogram showed them as an asymmetrical pattern in the majority of cases. Cancer infiltration into the seminal vesicles was detected on the tomogram in 6 out of the 8 cases of prostatic cancer (Fig. 7). The estimated volumes of the seminal vesicles were from 3·9 to 11·8 ml and of the prostates from were 31·5 to 43·6 ml.

Klinefelter's Syndrome. In the 5 cases of Klinefelter's syndrome, the seminal vesicles appeared at an average depth of from 5·5 to 3·5 cm from the anus. They were shown on the tomogram as symmetrical thin spindle shapes; but in every case the area was very small (Fig. 8). The estimated volumes of the seminal vesicles were from 0·1 to 1·0 ml and of the prostates were from 2·9 to 20·0 ml. Detailed results are given in Table I.

Table I

	Case No.	Seminal Vesicles		Prostate	
		Depth cm	Volume ml	Depth cm	Volume ml
Normal subject	1	7·0-3·0	18·1	3·5-1·5	22·3
	2	7·0-3·0	12·3	3·0-0·5	23·4
	3	8·5-4·5	14·8	6·0-3·0	13·2
	4	8·5-5·0	8·0	5·0-2·5	20·7
	5	9·0-4·5	12·5	5·0-2·0	25·4
	6	7·5-4·0	18·6	4·5-2·0	26·9
	7	7·0-4·0	11·8	4·5-2·0	18·8
	Average	8·0-4·0	13·7	4·5-2·0	21·5
Benign prostatic hypertrophy	1	6·5-5·0	8·6	5·5-2·0	73·9
	2	7·5-3·0	15·9	6·0-0·5	81·2
	3	7·0-4·5	7·3	5·5-2·0	47·0
	4	5·0-2·5	5·4	3·5-1·0	50·1
	5	4·5-2·5	5·1	3·0-0·5	44·2
	6	5·5-4·0	7·6	4·5-2·0	24·0
	7	6·5-2·0	7·9	4·0-0·5	45·0
	Average	6·0-3·5	8·3	4·5-1·0	52·2
Prostatic cancer	1	7·5-2·5	10·9	5·0-1·0	43·6
	2	4·0-2·5	6·0	3·5-0·5	31·5
	3	5·5-3·0	7·1	4·0-1·5	34·5
	4	8·5-3·5	5·8	5·0-2·0	37·6
	5	9·0-6·5	7·2	7·5-3·5	37·5
	6	8·0-3·0	9·0	5·0-2·0	41·2
	7	6·5-5·0	3·9	5·0-2·0	39·6
	8	7·0-4·5	11·8	5·0-2·0	34·2
	Average	7·0-4·0	7·7	5·0-2·0	37·5
Klinefelter's syndrome	1	4·5-2·0	0·1	4·0-2·0	11·9
	2	7·0-5·5	0·5	5·5-5·0	2·9
	3	4·5-4·0	0·3	3·5-2·0	6·5
	4	4·5-3·0	1·0	3·5-2·0	6·4
	5	6·0-3·5	0·6	3·5-2·0	20·0
	Average	5·5-3·5	0·5	4·0-2·5	9·6

Discussion

Ultrasonic measurement of prostatic size was first reported 4 years ago from our laboratory (Watanabe *et al.*, 1971).

Contact scanning from the abdominal surface has been also used to ascertain the prostatic size (Miller *et al.*, 1973). Only enlarged prostates could be measured in this way, however, as the ultrasonic beam is normally interrupted by the pubic bone. Since the seminal vesicles are much smaller than the prostate, it is very difficult to show them in this way. Moreover, when trans-abdominal compound scanning is performed manually, the direction of ultrasonic beam is so unstable that it is almost impossible to take parallel tomograms in as close a distance as 5 mm intervals.

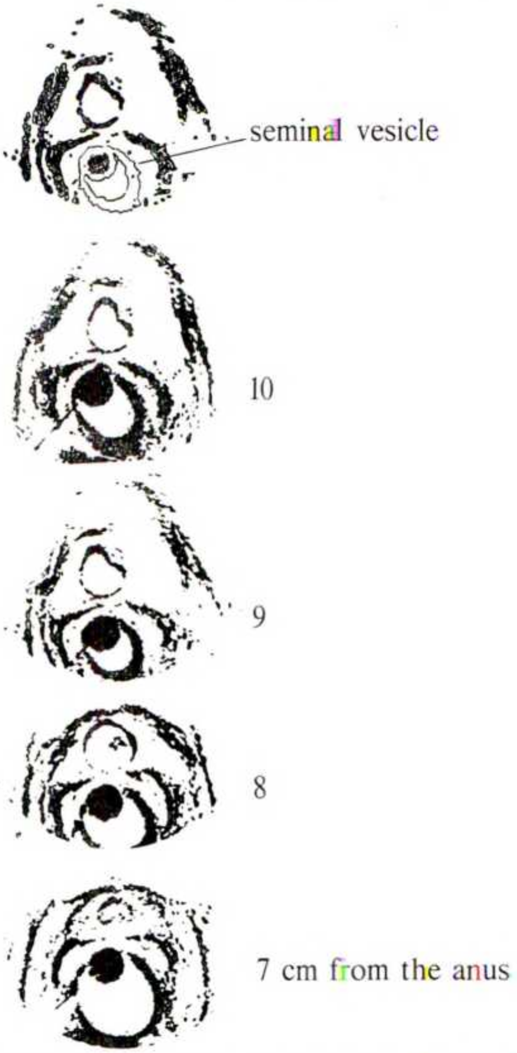

Fig. 5. Horizontal sections of the seminal vesicles in a normal case. The seminal vesicles are shown as two symmetrical spindle shapes between urinary bladder and the rectum in which the centre of the scan is shown. Inserted bag-catheter is also seen in the urinary bladder.

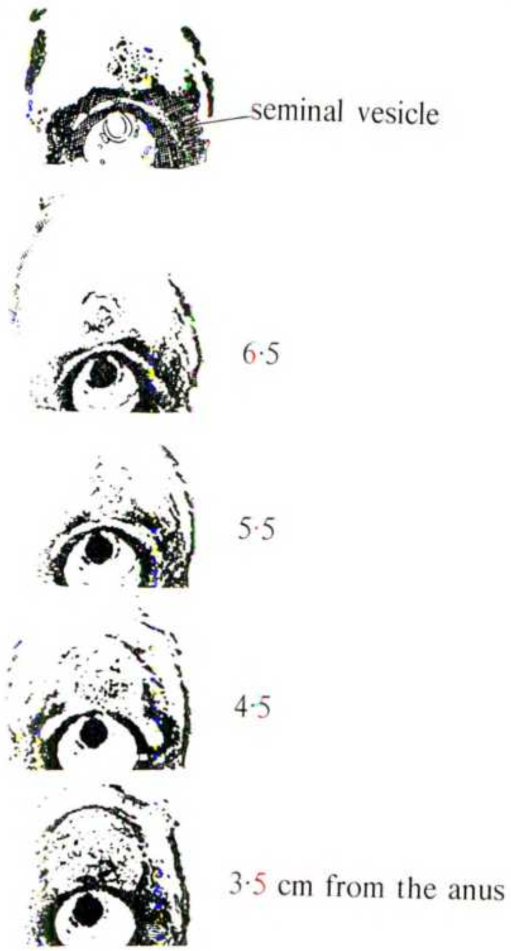

Fig. 6. Horizontal sections of the seminal vesicles in a case of benign prostatic hypertrophy. The seminal vesicles are shown as two symmetrical spindle-like shapes. Protrusion of the prostate into the urinary bladder is seen anterior to the seminal vesicles on the level of 5·5 cm. Only enlarged prostate is delineated on the level of 3·5 cm.

On the contrary, transrectal scanning in the sitting position makes it possible, for the direction of the probe is set up at a certain angle. For this reason, echographic examination in this study was achieved only by transrectal scanning in the sitting position.

X-ray studies (seminal vesiculograms) have shown the seminal vesicles rather enlarged than normal subjects in patients with benign prostatic hypertrophy and in some patients with prostatic cancer (Vestby, 1958; Fetter *et al.*, 1962).

Ultrasonic measurement, however, revealed that the volume of the seminal vesicles in normal subjects was approximately double the volume found in cases of benign prostatic hypertrophy or cancer.

Histologically the wall of the seminal vesicle consists of 3 layers: mucous membrane, thin layer of muscle and layer of connective tissue. The mucous membrane forms an intricate system of thin

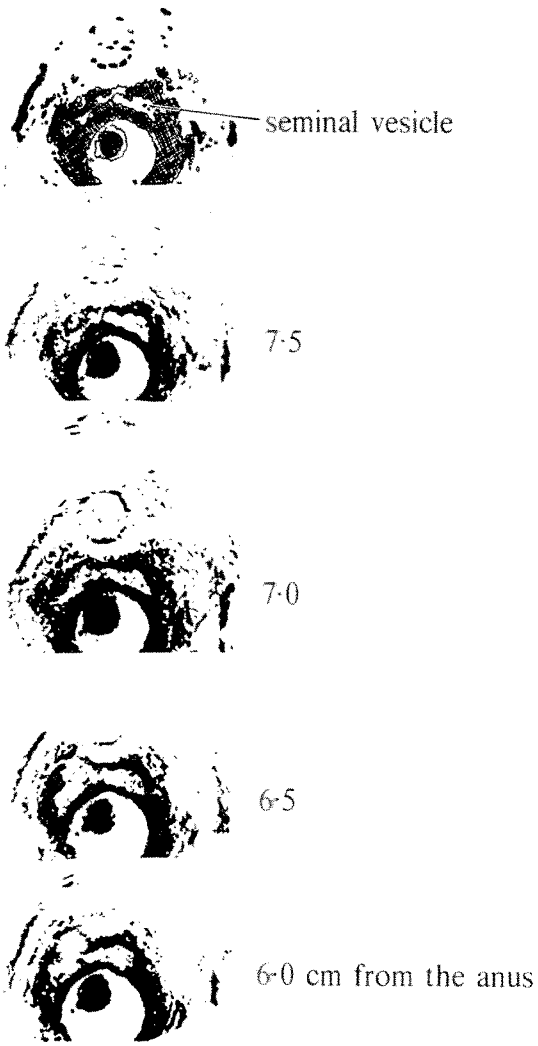

Fig. 7. Horizontal sections of the seminal vesicles in a case of prostatic cancer. The seminal vesicles are shown as an asymmetrical pattern. Cancer infiltration into the right seminal vesicle is seen in the left side of the picture on the level of 7·5 cm and 7·0 cm. Cystic dilatation of the right seminal vesicle probably caused by the stenosis of the ejaculatory duct is seen in the left side of the picture on the level of 6·5 cm and 6·0 cm.

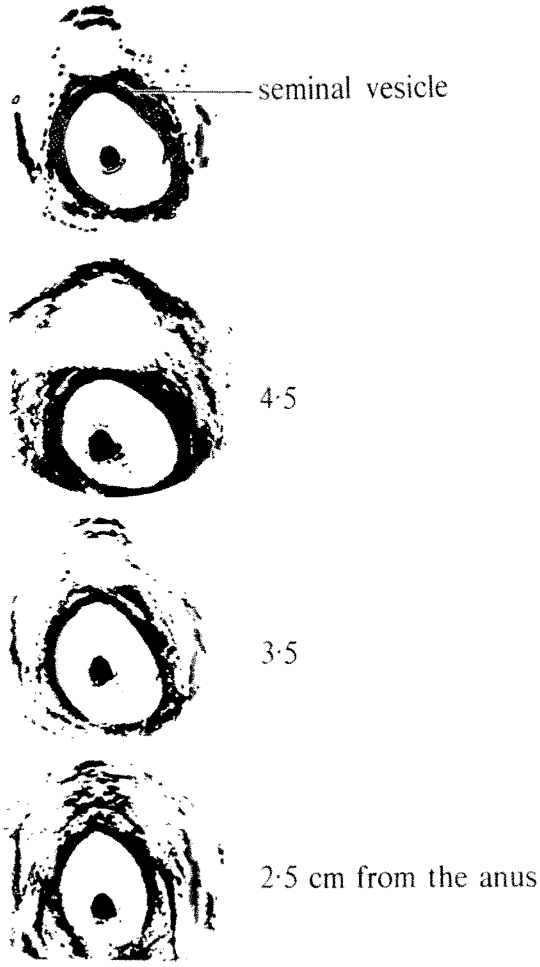

Fig. 8. Horizontal sections of the seminal vesicles in a case of Klinefelter's syndrome. The seminal vesicles are shown as a narrow slit-like pattern in the top and middle pictures. The prostate shown in the bottom picture is also very small.

primary fold. These folds project far into the lumen and anastomose frequently with one another. In this way numerous cavities of different sizes arise (Bloom and Fawcett, 1962).

Since these cavities are ordinarily filled with secretion from the seminal vesicles, it may be presumed that the contrast medium entering from the ductus deferens cannot always spread into the narrow peripheral lumen when seminal vesiculography is performed.

It is known that the epithelial cells of the mucous membrane degenerate in their capacity of spermato-genesis after castration in animals (Moore *et al.*, 1930). The same degeneration is often noticed in patients with prostatic hypertrophy or cancer. When this happens it seems likely that the contrast medium can easily get as far as the end of the lumen in these cases.

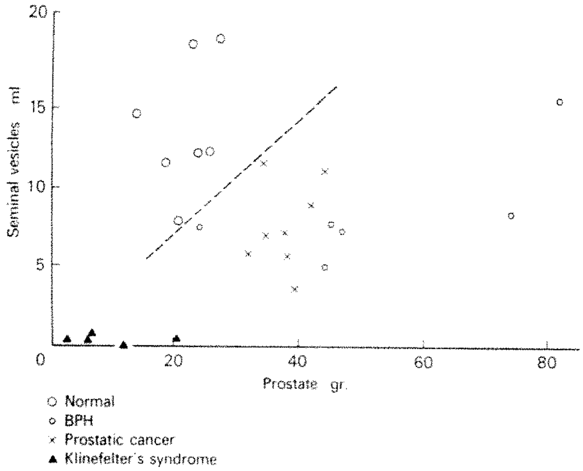

Fig. 9. Correlation between the volume of the seminal vesicles and the prostate. The ratio of the volume of the seminal vesicles to that of the prostate is higher in normal subjects than in cases of prostatic hypertrophy or cancer.

In normal adults the contrast medium would occupy only a part of the whole vesicles because the folds of the membrane are well developed and the lumen occupied by secretion.

It is thus probable that the area of seminal vesicles shown by seminal vesiculography does not represent the actual volume of the seminal vesicles in normal cases. On the other hand, in patients with benign prostatic hypertrophy or cancer, the contour of the seminal vesicles may well be closer to the actual size.

If this supposition is correct, then an accurate estimation of the seminal vesicles can only be done by transrectal ultrasonotomography.

Correlation between the volume of the seminal vesicles and the prostate is given in Figure 9. This shows that the ratio of the volume of the seminal vesicles to that of the prostate was higher in normal subjects than in cases of prostatic hypertrophy or cancer.

The volume of the prostate in Klinefelter's syndrome was generally found to be smaller than in normal subjects but it also became clear from this study that the volume of the seminal vesicles in this disease was much smaller and was no more than 4% of that found in normal subjects.

The diagnostic application of transrectal ultrasonotomography is very promising not only for the examination of the prostate or urinary bladder but also for the seminal vesicles, although the vas deferens and the ejaculatory ducts cannot be demonstrated by this method. It is hoped that details of the changes in the seminal vesicles shown by ultrasonotomography in various diseases will be reported.

Summary

The volume of the seminal vesicles was estimated in 27 cases by means of transrectal ultrasonotomography.

The seminal vesicles of normal subjects were found to be generally larger than in cases of prostatic hypertrophy or cancer. The volume of the seminal vesicles in Klinefelter's syndrome was remarkably small.

The correlation between the volume of the seminal vesicles and of the prostate is given.

The authors are indebted to Professor Sentaro Shishito for his guidance. This work was supported by a grant for cancer research from the Welfare Ministry of Japan.

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ABSTRACTS FROM CURRENT UROLOGICAL LITERATURE

British Journal of Radiology

By Charles Nicholas

"The Radiological Diagnosis of Adrenal Tumours." David Sutton (1975, **48**, 237-258)—13 cases of Conn's tumour were diagnosed by adrenal phlebography and 18 phaeochromatocytomas were investigated by anteriography at St Mary's Hospital Department of Radiology. After preliminary notes on adrenal syndromes radiological methods appropriate to the investigation of each are described and details of technique given. Plain X-rays and IVP may show large tumours and downward displacement of the kidney but arteriography is necessary to differentiate between renal and adrenal tumours. In the investigation of Cushing's syndrome adrenal phlebography is more accurate in demonstrating tumours than retroperitoneal air insufflation and it is now possible to catheterise the adrenal veins on both sides. Selective adrenal arteriography and radioactive isotope scans have proved useful. Large phaeochromatocytomas are demonstrated by air insufflation and tomography including lateral views. Both selective renal arteriography and flush aortography have been found safe providing phentolamine is readily available during the radiological investigation. Avascular phaeochromatocytomas, multiple and ectopic tumours still present difficulties. Case histories and many clearly reproduced X-ray pictures are included in the article.

"Changing Etiologic Patterns of Renal Insufficiency in Surgical Patients." Ronal P. Fischer and Hiram C. Polk, Jr. (1975, **140**, 85-86). In this Editorial, the authors from New Mexico and Kentucky maintain that today the commonest cause of acute renal failure is Gram-negative septicaemia rather than the ischaemia associated with haemorrhagic shock and other causes of hypotension. They emphasise that by careful clinical history and examination and special investigations as necessary, the site of the infection, which is often intra-abdominal, should be localised and radically treated.

Surgery Gynecology and Obstetrics

By Thomas Moore

"Factors Influencing Morbidity and Mortality of Renal Transplantation in a High Risk Population." Joshua Miller, George Kyriakides., King W. Ma, Donald Masler and David C. Brown. (1975, **140**, 1-6.)—The authors reported their results of renal transplantation in 37 cases, 32 of whom, because of diabetes, considerable cardiovascular, gastrointestinal, cerebrovascular, pulmonary disease or age, over 45 years, were regarded as severe risks. Only 2 patients in this group died and the transplant survived in 92%. The authors believe that evaluation of pre-transplant mixed lymphocyte cultures, HL-A antigen and immune responder status; close follow-up observation of lymphocyte culture and humoral responses by in vitro testing and the use of antilymphoblast globulin are the reasons for these excellent results.

"Renal Hypertension". Alexander M. C. MacGregor and James R. Cade. (1975, **140**, 97-110.)—In a study of the literature with 248 references from Bright's to recent times, the authors review the aetiology, pathophysiology, clinical features, screening tests, which include rapid sequence excretory urography, isotope renography and arteriography, tests of renal function, including differential renal function tests, differential renal vein renin, prognosis and treatment.

"Treatment of Accelerated Hypertension and End Stage Renal Failure by bilateral Nephrectomy and Renal Transplantation." A. G. Diethelm, M. W. Hartley, J. S. Aldrete, W. A. Sterling and J. M. Morgan. (1975, **140**, 161-169). From the University Medical Center and the Birmingham Veterans Administration Hospital, Alabama, the authors report on the treatment of accelerated hypertension in 22 cases, which did not respond to haemodialysis and ultra filtration, treated by bilateral nephrectomy. In 5 patients operation was carried out as an emergency. Normotension was restored in every case but hypertension returned in 12 patients after renal transplantation for which medical treatment was required. The authors were unable to identify any feature which could forecast the occurrence of post-transplant hypertension.

"What's New in Surgery—Urology." Birdwell Finlayson, (1975, **140**, 224-227.) This is the review of Urology presented at the 16th Annual Clinical Congress of the American College of Surgeons at which a full bibliography was available. The subjects discussed included: The clinical and morphological ultrastructure of the transitional epithelium lining the urinary tract. Investigation of urodynamics using an air displacement urine flow meter. Use of a urodropspectrometer in the study of urinary dynamics. The effect of 5-thio-D-glucose on spermatogenesis. The effects of intraperitoneal pancreatic transplants on diabetic lesions in the kidney. The complement fixating tumour antigen present in the urine of patients with carcinoma of the bladder. Radio-immunoassay for Beta sub-units of plasma human chorionic gonadotropin in patients with tumours of the testes. Transplantation of cancer cells into normal epithelium. The effect of norepinephrine on bladder muscle. Work showing that colonic urinary conduits are associated with less ascending infections than are ileal urinary conduits. The use of angiography in locating retroperitoneal testes. The effect of clomiphene citrate in oligospermia. Estimation of residual urine by using I.131 Hippuran and bladder scanning for radioactivity after micturition.

"Clinical and Roentgenographic Evaluation of Endoscopic Suspension of the Vesical Neck for Urinary Incontinence." Thomas A. Stamey., Anthony J. Schaeffer and Mercy Condy. (1975, **140**, 355-360.) From the well known Urological Centre in Stanford, California, Dr Stamey and his team report the results of 44 patients thought to be suffering from pure stress incontinence, treated by suspension of the urethra by monofilament nylon slings, one on each side of the bladder neck, to the rectus sheath through a suprapubic exposure. To ensure that the sutures are placed exactly at the urethrovesical junction and do not penetrate the lumen, the area is viewed through a right-angle cystoscope during their insertion. Full details are given of the careful pre- and postoperative radiological studies by lateral cystograms of each case and the criteria by which the authors diagnose the condition and assess the results of operation. All patients showed substantial upward and forward elevation of the urethrovesical junction as measured by the urethrovesical angle, the angle of urethral inclination and elevation of the base of the bladder. In spite of a complaint of urgency in many patients as well as 44 previous gynaecological operations in 22 of them, cystometry and other functional tests revealed no case of the so-called unstable bladder. 41 patients were cured and, of the 3 in whom the treatment failed, 2 did not have the typical pre-operative radiological findings.

"Further Experience with Circle Tube Nephro-ureterostomy Urinary Diversion." THOMAS A. BORDEN, WILLIAM B. GILL and EDWARD S. LYON. (1975, **140**, 547-548.) The method consists of draining the kidney through a silicone tube which passes through the loin through the cortex of the kidney, down through the pelvis and transected ureter and out through a wound lower in the loin. The two ends are joined by a "Y" piece to a single drainage tube into a bag. That part of the tube in the pelvis and calyces has several holes cut in its wall. This so-called circle tube nephro-ureterostomy has been used by the authors in 80 patients for a wide variety of urological problems.

"Technique and Results in Fifty-five Open Renal Biopsies in Children" JOHN D. BURRINGTON (1975, **140**, 613-614). From the Chicago Childrens' Hospital the author reports his technique for open renal biopsies in children. With the patient under general anaesthesia and prone over a kidney bridge, a vertical incision 2 to 3 cm long is made through the fascial tissues just lateral to the sacrospinalis muscle from the lower border of the 12th rib downwards and the lower pole of the previously radiologically located kidney is exposed. Using a disposable biopsy needle, a specimen is taken from the kidney under direct vision. The 55 biopsies taken from 47 seriously ill children contained from 9 to 93 glomeruli in each and from all accurate diagnosis could be made. There were no significant complications.

New England Journal of Medicine

By J. L. ANDERTON

"Carcinoma of the Urinary Bladder in Patients receiving Cyclophosphamide." ROBERT L. WALL and KATHRYN P. CLAUSEN. (1975, **293**, 271-273.)—The authors from Ohio State University College of Medicine report 5 cases of carcinoma of the bladder following prolonged use of cyclophosphamide (3 to 15 years), the outcome being fatal in 4 cases, and requiring total cystectomy in the remaining case.

Haemorrhagic cystitis is a well known reversible complication of cyclophosphamide therapy but these 5 cases with the 5 already reported in the literature reinforce the need for vigilance in the management of patients receiving cyclophosphamide for long periods.

Surgery

By R. T. BURKITT

"Renal Autotransplantation and Partial Resection of the Ureter for Recurrent Benign Ureteral Tumor." E. C. SALTZSTEIN and S. W. FINE. (1975, **77**, 607-611.)—A young patient is described who had a diseased right kidney due to obstruction associated with duplicated ureters and an ureterocoele. She subsequently developed recurrent ureteric polypi on the other side, necessitating extensive ureteric resection. To avoid sacrificing this healthy kidney it was removed and re-implanted in the left side of the pelvis, with an apparently excellent functional result.

Deutsche Medizinische Wochenschrift

By John Grieve

"Human Menopausal Gonadotrophin in the Treatment of Infertile Men." D. SINA, H. D. TAUBERT, and R. KARSCHNIA. (1974, **99**, 2639-2643.)—Treatment with HMG or HMG and HCG was given to 38 men with oligospermia. In 19 patients there was improvement, 17 were unchanged and 2 deteriorated in relation to the sperm count. Those treated by the combined therapy showed the greater improvement. 12 of the patients in this latter group showed a definite improvement and 5 were unchanged. 9 wives became pregnant after treatment of ovulatory disorders with HMG and clomiphene. It is interesting to note here that the sperm counts among successful fathers were very variable.

"Endocrine and Histological Investigations in Testicular Atrophy associated with Myotonic Dystrophy. H. BECKER and N. HOFMANN. (1975, **100**, 149-152)—Testicular atrophy in myotonic dystrophy is caused by a primary and progressive atrophy of the seminiferous tubules. Endocrine tests with synthetic LH(ICSH)-RH in 2 patients demonstrated the complete absence of FSH feedback mechanism. The glycogen content was markedly reduced or absent to histochemical testing both in morphologically normal and damaged tubules. The endocrine and morphological results show that Sertoli cell insufficiency is the first stage in the pathogenesis of testicular atrophy in myotonic dystrophy.

La Nouvelle Presse Medicale

By John Grieve

"Gonadal insufficiency related to Prolactin." G. KANN, G. STRAUCH and J. C. VALCKE. (1975, **4**, 639-640)—Hypersecretion of prolactin may be responsible in both sexes for gonadal insufficiency, the mechanism of which is poorly understood. These examples of hypogonadism require careful definition and their frequency estimated. This information is important because the gonadal upset may regress with a return to normal of prolactin secretion and because effective and simple antiprolactin therapy is now available.

"Hormone Dependence of the Human Prostate and Prostatic Adenoma." J. P. BERCOVICI, R. MORFIN and J. F. CHARLES. (1975, **4**, 475-478.)—Prostatic adenoma develops at the site of the peri-urethral glands. The concentration of 5α dihydrotestosterone seems greater at the centre of the adenoma than in the overlying prostate. The authors from Brest suggest that medical treatment of prostatic adenoma might be feasible using substances inhibiting the 5α reduction of testosterone.

Conferences and Courses

UROLOGICAL SOCIETY OF AUSTRALASIA

The 29th Annual General Meeting will be held in Hong Kong, 21st to 25th March 1976. The Scientific Session will be in the Queen Mary Hospital, Hong Kong.

There is the possibility of a one-day Meeting on Monday, 29th March, at Kuala Lumpur to follow.

For further details write: H. M. Learoyd, 64 Denistone Road, Eastwood, NSW 2122, Australia.

INTERNATIONAL SYMPOSIUM ON URINARY STONE FORMATION

Davos, Switzerland, 29th March to 1st April 1976
The presentations and discussions will be in English.

Further information from: Prof. H. Fleisch, Department of Pathophysiology, Murtenstrasse 35
CH—3008 Bern, Switzerland.

SYMPOSIUM ON EXPERIMENTAL UROLOGY

The 3rd Symposium on Experimental Urology will be held in Wurzburg, West Germany on the 1st to 3rd April 1976. Further details obtainable from Dr F. H. Schroder, University Urological Clinic, Luitpold-Krankenhaus, 87 Wurzburg, Joseph-Schneider-Str. 9.

INTERNATIONAL COURSE OF UROLOGY

Barcelona, April 1976

The 7th International Course of Urology will be held in the 2nd week of April 1976 and will last 5 days. There will be simultaneous translation into English, French, German and Spanish.

Detailed information available from: Department of Urology Secretary, School of Medicine, University of Barcelona, Casanovas 143, Barcelona-11, Spain.

THE THIRD INTERNATIONAL SYMPOSIUM ON DETECTION AND PREVENTION OF CANCER.

To be held at the Americana Hotel in New York City from 26th April to 1st May 1976. The Scientific Program deals with detection and prevention of tumour development by identification of environmental, occupational, genetic and other risk factors.

For detailed information, contact: Herbert E. Nieburgs, M.D., Mount Sinai School of Medicine, Fifth Avenue at 100th Street, New York, NY 11029, USA. Tel: (212) 534-4991.

SECOND CONGRESS OF THE EUROPEAN ASSOCIATION OF UROLOGY.

This Congress will be held from 24th to 26th September 1976, in Prague, Czechoslovakia.

Scientific Programme:

1. Lymphadenectomy in urologic cancers.
2. Urogenital tuberculosis, current state in Europe.
3. Free communications and films.

Active participation in the Congress is limited to members of the European Association of Urology only.
Inquiries to be sent to: Urology '76 Secretariat, Sokolska 31, 120 26 Praha 2, Czechoslovakia.

Book Reviews

Urinary Incontinence. Edited by K. P. S. CALDWELL. Sector Publishing Limited. 1975. £6·00

There is a pressing need for monographs of this nature. Our understanding of bladder physiology has changed so much in recent years that the urologist is unable to communicate adequately with his colleagues in other specialities. The chief sufferer is only too often the patient.

A distinguished panel of contributors ensures that the problem of incontinence is discussed in an authoritative and attractive manner. A particularly valuable feature is the historical approach made by each contributor—there is also an invaluable chapter on the history of urodynamics by Doyle—which lends a vitality often lacking in the more usual dogmatic textbook. The critical reader can perceive some of the gaps in our knowledge, which are many, and some of the doubts in our hypotheses. At the same time, he cannot but be helped in his development of a rational approach to therapy and in his management of the individual patient.

Inevitably, in a subject such as this, there are imperfections. The major problem lies in the scope of the book itself. Incontinence is only one possible manifestation of many different varieties of dysfunction. It is essential to try to relate the symptom of incontinence to the problem of bladder function as a whole. The opening chapter on the problem of incontinence starts in this direction but ends with a classification which includes such headings as "Gynaecological incontinence" or "Traumatic incontinence". Such terms surely should be discontinued and replaced by an analysis of the functional disturbance. One other major criticism of this book must be of the section on geriatric incontinence. Although there is an excellent description of the management of the patient who is wet, there is little indication that the incontinent old patient can often be cured, and frequently by very simple means. Although there is a group of patients in whom cure will never be possible, our initial attitude must be how to make the patient dry rather than which is the best appliance.

It is too easy to find holes in a book related to a subject such as bladder dysfunction where our ignorance is enormous. Too many patients suffer needlessly from incontinence. The authors are to be congratulated on a book which should be read by any doctor who may have to manage an incontinent patient.

D. M. E.

Proceedings of The Fifth International Congress of Nephrology, Mexico 1972. Edited by Herman Villareal. Basle; Karger, 1974. Volume 1, Morphology and Pathology, pp. 188+xvl, 31 figs., £9·10. Volume 2, Physiology, pp. 202+xvi, 73 figs., £9·10. Volume 3, Clinic pp. 313+xvi, £9·10. Set of three in case, £23·30.

Nephrologists are enthusiastic attenders of international meetings. Many of these like the ASAIO, the EDTA, the annual Contractors' conference of the NIH and the new European Society for Artificial Internal Organs meet annually, publish their proceedings, consisting largely of original work, with great rapidity and also publish abstract volumes which have become media of communication. Any symposium on practical nephrology (*e.g.*, the recent Kidney International supplement on adequacy of dialysis) is bespattered with references to these proceedings, the abstracts of the American Society of Nephrology and the Clinical Dialysis and Transplant Forum. The International Society of Nephrology has a different function. The Proceedings contain some original work but their main function is to reproduce the "state of the art lectures", plenary sessions and symposia which attempt to give a broad view of nephrology during the meeting. Their success must be judged firstly by how often the delegates go back to the Proceedings to refresh their minds on what they learned. I can only assess this at the personal level; I have made very good use of the Proceedings of some conferences, *e.g.*, Washington 1966 and my reading of the present set suggests that it will be equally valuable.

It is a great pity that these Proceedings appeared more than 2 years after the meeting and this review will be read when delegates have returned from the next international congress of nephrology, having heard a new set of "state of the art" lectures. It is also a shame that the elegant format adopted by Karger for all their publications limits the space available so that few of the reviews are really comprehensive. I am convinced they should change to a quick publication, with economical use of space in future editions.

However, there are some excellent reviews in the "Mexico Proceedings" which will justify purchase of the set by those libraries that have not felt the economic draught too badly. In the Morphology and Pathology section Wilson has a succinct summary of immune complex nephritis which has not been dated by subsequent work though the list of antigens in human disease is a lot shorter than the one his colleagues showed at Florence. Monaco provides a well written introduction to immunological tolerance and enhancement and Bach reviews the immunological follow-up of the transplant patient. The Physiology volume opens with a review of the metabolic fuels of the kidney by Robert Pitts and deals in detail with transport processes in the tubules, micro-puncture techniques and the postulated natriuretic hormone.

Volume 3 contains more of direct relevance to urologists. There is an interesting section on proteinuria with a particularly helpful review by Robinson on asymptomatic proteinuria. Baldwin has a comprehensive section on the natural history of acute nephritis. There are good symposia on regular haemodialysis, hypertension in renal disease and a particularly good section on renal bone disease. Urinary infection receives less attention than it deserves but Fairley has some interesting observations on the site of urinary infections. Greifer presents the results of the International Study of Kidney Disease in Children (an important study whose authors seem otherwise reluctant to appear in print). Finally Merrill predicts a future for nephrology which makes no mention of the existence of urologists (except by implication as the inserters of transplants). However, in the 3 years since he gave the lecture we have not advanced far enough along the road to suggest that urologists should start retraining as geriatricians.

D. N. S. K.

Acid-base and Electrolyte Balance. Gosta Rooth. pp. 118. Wolfe Medical Publications Ltd., 1975. £3·25.

The subject of acid-base balance is made confusing to most doctors by a difficult terminology and by the presentation of complicated mathematical formulae. This book is based on the author's teaching to doctors, medical students and other groups, and perhaps because of this he has succeeded in keeping the subject simple and comprehensible.

In a few places simplification has led to confusion; for example, a mathematical explanation of the Donnan equilibrium would have helped in explaining differences referred to in plasma and interstitial fluid composition. A potent cause of confusion arose in his definition of base excess in Chapter 1 as base to restore pH to normal at PCO2 40 and in Chapter 5 as acid to restore pH. His simplification of mathematical relationships by the use of approximations is useful in giving an understanding of the subject but, as he himself points out, the approximations become invalid in the very situations in which we need the information and I think, on balance, would have been better left out.

In summary I think that it is a useful, readable little book of value to undergraduates and practising physicians.

R. W.

New Encyclopedia of Surgical Technique. Volume 15. Urology and the Male Genital System. R. COUVELAIRE and J. CUKIER. pp. 845 with 993 illustrations. Paris, Masson et Cie. 1974. 335 francs.

This well produced and well illustrated volume covers the main operations in urology and the male genital system very systematically. The 12 chapters start with general considerations and then deal with renal surgery, renal artery surgery, renal transplantation, surgery of the renal and neighbouring lymphatics, the conservative surgery of the excretory passages, the surgery of the ilio-pelvic ureter, of the bladder and bladder neck and prostate and of the male urethra. The last 2 chapters deal with the female bladder neck and urethra, and with the testis and related structures. There is a refreshing simplicity about the illustrations which are all black and white and in the setting out of the instructions for carrying out various operations.

An unusual feature of this volume is the frequent statement of the aim of the operation coupled with the consideration of the technique most likely to be helpful in particular circumstances. The text is easy to read and the book should be of especial value to the urologist in training as a reference work in surgical technique, and also of use to the practising urologist as a way of refreshing his memory on forgotten details of less commonly practised operations. The two authors have contributed an excellent volume to the encyclopedia.

J. G.

The Biology and Clinical Management of Bladder Cancer By E. H. COOPER and R. E. WILLIAMS. pp. 293+x with 51 illustrations and 46 tables. Oxford: Blackwell Scientific Publications, 1975. £9·75.

"Eight contributors from Europe and the United States have joined together to write a comprehensive monograph on bladder cancer . . . they present the lessons they have learned from the past . . . and identify the many problems yet to be solved."

This is essentially a practical book (despite the many rodents gnawing at the chemical formulae in the opening chapter) for the collective experience of the contributors is considerable. The chapters dealing with epidemiology and carcinogenesis are rather repetitive but provide extensive reference material. The biology, refreshingly, is that of human bladder tumours and reviews the current understanding of bladder tumour growth, cell kinetics, cytogenetics, electronmicroscope appearances and histochemistry. The histopathology is commendably simple and the technical details of urinary cytology and the description of the urinary sediment are very welcome, if rather belated. Immunology is brief as befits our ignorance of this particular aspect of bladder cancer.

The second and most valuable half of the book debates the controversy of clinical management. "Carcinomas of the urinary bladder are potentially radiocurable. . . . Total cystectomy is often regarded as an operation of defeatism. . . . Too much emphasis on (pathological) terminology and not enough on biology. . . . In future cytology will replace biopsy as a basic diagnostic method." Comments such as these guarantee fascinating reading. The problems are not solved, but there is much food for thought.

The illustrations could be better, and there are too many printing errors. Despite this the book gives good value for money: buy one—and perhaps give another copy to your pathologist!

R. R. H.

Reviews in Paediatric Urology. Ed. by J. H. JOHNSTON and W. E. GOODWIN. Pp. X+482 with approx. 300 illustrations. Amsterdam: Excerpta Medica. 1974. £22·10.

In their introduction the editors state that paediatric urology is attaining the rank of a specialty in its own right. A survey of the subjects covered by this book should convince the reader that it is time that this state of affairs had materialised on a more widespread basis: it is made quite clear that children with urological disease have complex problems relating both to their urinary tracts as well as to the general implications of illness in children and that their management should only be in the hands of surgeons with special experience in this field.

The book bears the title of "Reviews" in paediatric urology but some of the chapters do not substantiate this claim. The chapters on urinary diversion are, by and large, simply descriptions of operative technique (there is no discussion on uretero-sigmoidostomy or the long-term effects of uretero-ileostomy) and the chapter on renal hypertension could have been more concise without losing its informative value by excluding the case reports. Apart from these criticisms each contribution is clearly written by an author with wide and detailed knowledge of his subject and their accounts are comprehensive and readable. The chapters on renal transplantation and testicular tumours are particularly well written and the chapter on compensatory renal hypertrophy is a fascinating review of the experimental work that has been done on this subject.

All those who aspire to enter the field of paediatric urology should have this book to refer to during their training: those who feel they have already arrived will discover a store of valuable information in its pages.

J. E. S. S.

Urologic Surgery. Ed. by JAMES F. GLENN. 2nd ed. Pp. XXV+1018 with 777 illustrations. New York: Harper & Row. 1975. $65.

This book comprises 71 chapters written by as many eminent urologists with the objective of writing explicitly about the technical details, the problems and rationale of specific urologic procedures.

Each chapter is prefaced by a salutary reminder of the relevant history, anatomy, embryology or physiology. This is welcome. Then follows a great deal of valuable factual information and interesting surgical opinion but some of the rather all-inclusive descriptive prose sometimes makes heavy reading. With 149 pages devoted to various aspects of renal surgery and its complications it was puzzling to read that "a detailed discussion of the postoperative care of the patient subjected to renal surgery is beyond the scope of this text". There is also some unnecessary duplication (or triplication) of operative descriptions. For example, transureteroureterostomy is described on 3 occasions together with nearly identical illustrations in the chapters entitled Ureteral Surgery, Ureteral Diversion and Ureteral Substitution. It is recognised that the different accounts are by different authors, but the point of comparing personal techniques is easily missed by the presentation.

The illustrations are plentiful, pleasing to the eye and sometimes very helpful. On the other hand, some are inappropriate (what has a picture displaying the discomfort of vesical exstrophy to do with sigmoid conduits?) and others are unrealistic (a kidney which requires subcapsular nephrectomy should not be illustrated as a smooth organ in the palm of the surgeon's hand outside the wound) or unnecessary—the reader of such an advanced textbook should not need an illustration to show the difference between sharp and blunt dissection of the ureter.

One of the attractions of this comprehensive text is its multiple and varied authorship and despite the above criticisms, many will welcome this volume for the information and diversity of opinion which it presents.

R. R. H.

Urinary Diversion Stomas: A Guide for Patients and Nurses. By EILEEN M. SPRAGGON. 2nd ed. Pp. X+41 with 27 illustrations. Edinburgh: Churchill Livingstone. 1975. £1·00.

This second edition is a considerable advance on the first in that it deals with disposable urinary diversion appliances and has a chapter on the special problems of children with spina bifida. The book is based on the author's own experience as a stomatherapist to the Urology Department of Newcastle General Hospital.

Clearly written and well laid out, it contains a mine of information about appliances of the semi-disposable and disposable type, the technique of appliance management, and skin care, all of which are problematical. The illustrations are excellently chosen to demonstrate the technique and attention to fine detail involved in changing appliances.

Patients can easily make reference to their particular problem by referring to the excellent table of contents. Although written primarily for patients and nursing staff, a good deal of patient misery would be spared if the contents were common knowledge to those doctors with stoma patients under their care. No urology ward or outpatient clinic should dare be without a copy.

R. N. P. C.

Drugs and the Kidney. Ed. by K. D. G. EDWARDS. (Progress in Biochemical Pharmacology, Vol. 9.) Pp. xi+274 with 64 illustrations. Basel: Karger. 1974. £17·60.

This volume follows the usual pattern in this series. It consists of 20 different papers on selected topics. They are mostly of high quality and are of considerable interest to the practising physician. The subjects include micropuncture studies in the rat to demonstrate the intrarenal action of furosemide and its site of action in the nephron, the renal action of dopamine and its possible clinical applications, the effects of propranolol on blood pressure and plasma renin activity and the mechanisms of intravascular coagulation. The section on cyclophosphamide in the treatment of glomerulonephritis other than minimal change lesions, purports to show benefit when no controlled trial was performed and this must be regarded as the weakest and most misleading section of the book. There is a good section on antilipemic drugs in nephrotic syndrome which emphasises the importance of the antagonism existing between cholestyramine and clofibrate. Also of considerable interest is the effect of hypertriglyceridaemia in the enhancement of transplant rejection. This effect can apparently be reversed by antilymphocyte globulin.

The section on drug side-effects includes evidence of renal tubular damage from co-trimoxazole in normal doses given to patients with chronic renal failure.

There is a good section on drugs affecting the renal handling of urate, including, of course, allopurinol. Dr Blagg from Seattle gives a concise summary of current advances in techniques for regular dialysis including the portable machine employing a sorbent-based dialysate regeneration system. Finally, a short paper describes successful treatment of apparently refractory hypertension in 4 patients by proper attention to adequate sodium deprivation.

The book is well bound and printed on high quality paper but the high price of £17·60 is barely justified by the amount or quality of useful information it contains. One imagines that few private individuals will feel able to afford it.

The Mammalian Kidney. By D. B. MOFFAT. (Biological Structure and Function 5.) Pp. viii + 263 with 77 illustrations. Cambridge: Cambridge University Press. 1975. £9·00.

To reconcile renal morphology and function is an endeavour which all interested in the kidney must applaud. Professor Moffat's approach to this sisyphean task is firmly based in morphology with a strong emphasis on ultrastructural studies in man and animals. In addition the enormous literature on experimental physiology has been extensively reviewed. References are not comprehensive but reviews and key references are quoted. In 12 chapters each of the structural components of the kidney is described and the functional significance discussed. In a final chapter new ultra-structural techniques are described, and the direction of further advances is indicated.

The book is directed to senior undergraduates and research workers in many disciplines. Clinicians may find the morphological emphasis excessive, but it is evident that functional and morphological concepts must be combined for further advances in our understanding of the kidney. Histopathologists will welcome this approach, but will deplore the method of reproduction, which has marred many excellent micrographs. Diagrams are excellent but greater use in the explanation of theoretical concepts would have been valuable.

A. R. M.

Books Received

Inherited Biochemical Disorders and Uric Acid Metabolism. By D. S. NEWCOMBE. Aylesbury: HM + M Publishers Ltd., 1975. £12·00.

Tumors of the Urinary Bladder. L. G. KOSS, (Atlas of Tumor Pathology, 2nd series, fasc. 11). Washington: Armed Forces Institute of Pathology, 1975. $8.00.

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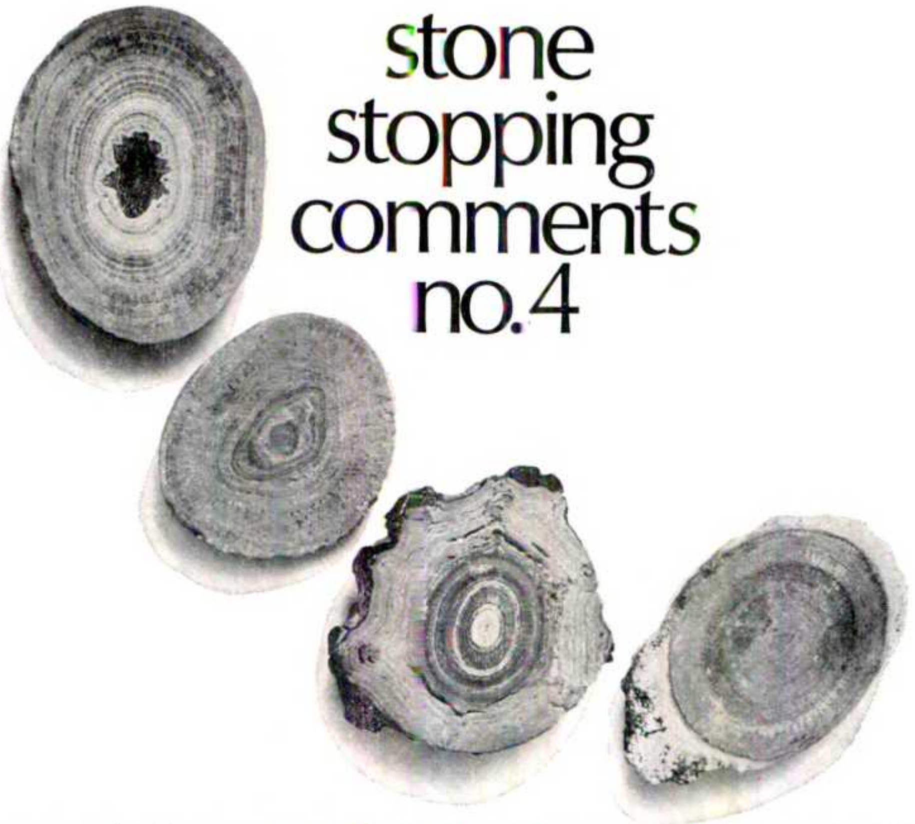

In a recent study[1] measurements of ^{47}calcium and of urinary calcium excretion were made in 125 cases of urolithiasis (78 solitary stone, 47 recurrent).

The authors found that 57 out of 60 patients with hypercalciuria showed raised absorption of ^{47}Ca, whereas 49 out of 106 patients showing similar hyperabsorption of calcium had *normal* calcium excretion. The authors concluded that "...a majority of stone formers, whether they are hypercalciuric or not, absorb calcium excessively from the intestine and this is more prevalent in cases of recurrent urolithiasis."

As a sequel to investigation 1, the same authors[2] studied the effect of Sodium Cellulose Phosphate on intestinal calcium uptake. In comparison to a low calcium, low oxalate diet; "Sodium Cellulose Phosphate can significantly diminish the absorption of calcium from the intestine; there is concomitant diminution of urinary calcium excretion. The plasma levels of the divalent cations do not appear to be influenced by this therapy."

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In terms of side-effects and toxicity, the authors stated "Serum levels of calcium and phosphorus were not altered in any of the patients even when the substance had been taken for a period as long as 7 years in a dose of 5g 3 times daily." There was no diarrhoea or intestinal disturbance, and patients found SCP reasonably palatable and easy to take.

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1. Brit J Urol, (1974) **46**: 377-384.
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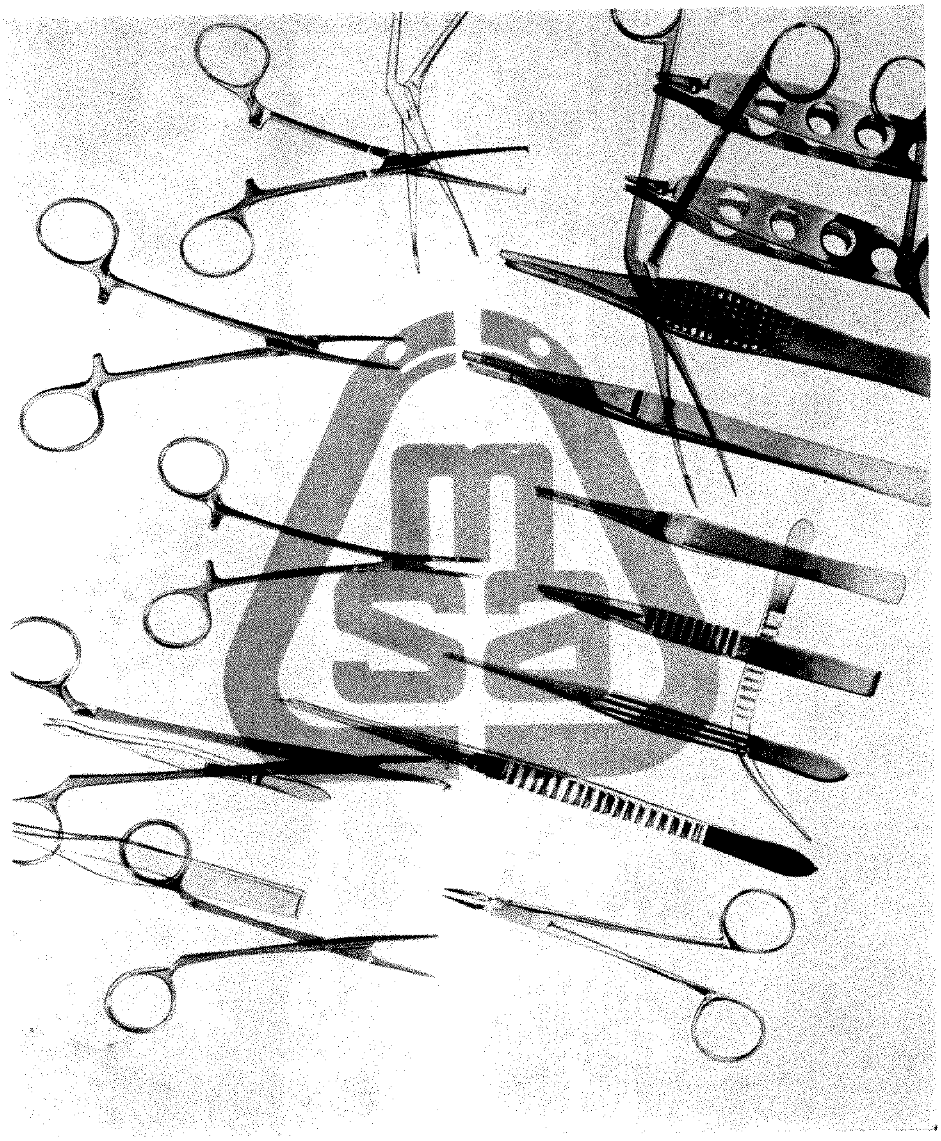

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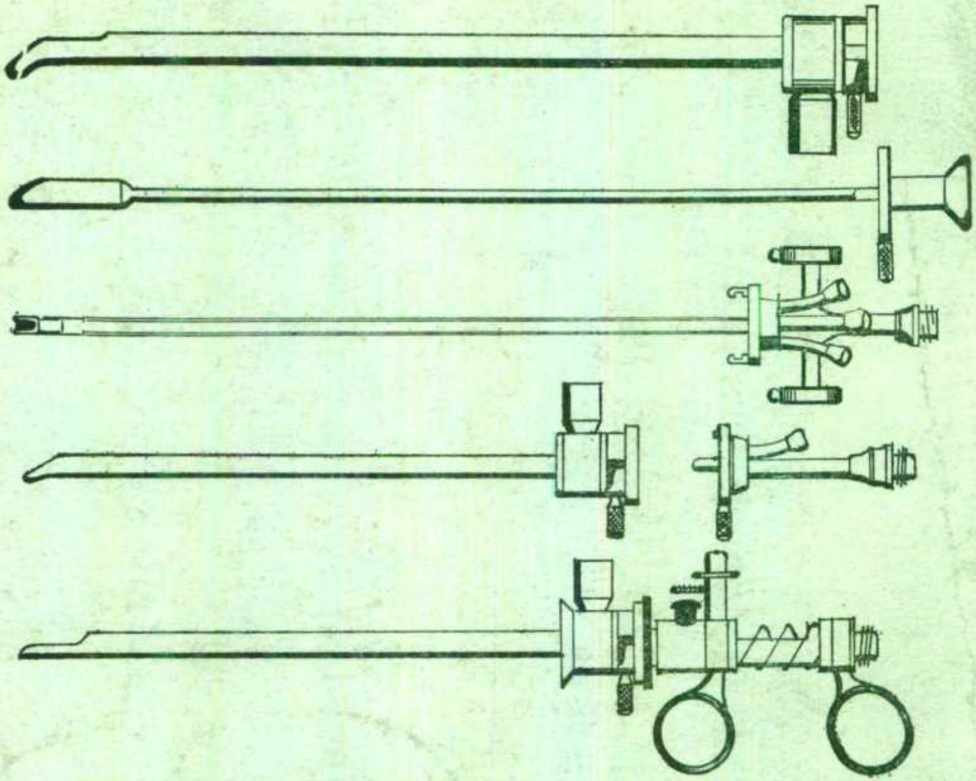

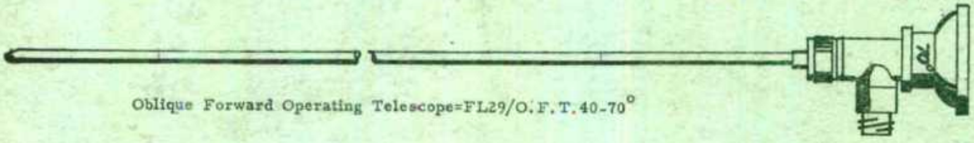

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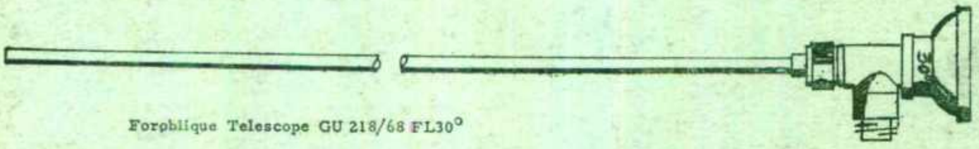

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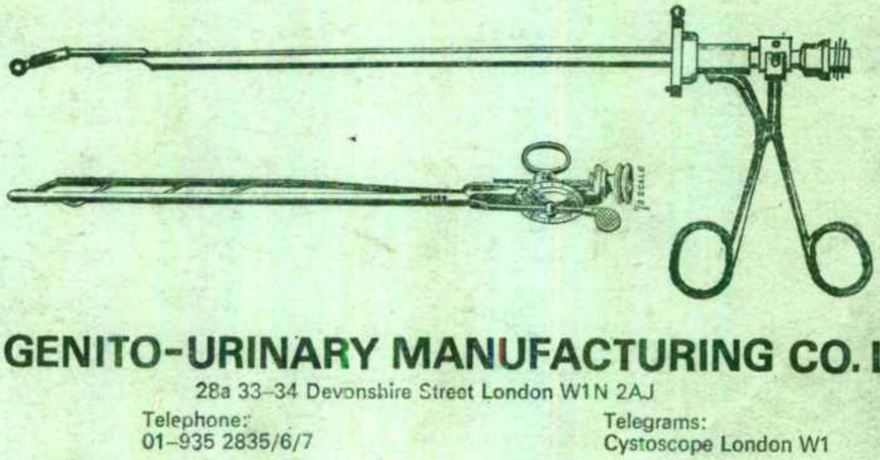

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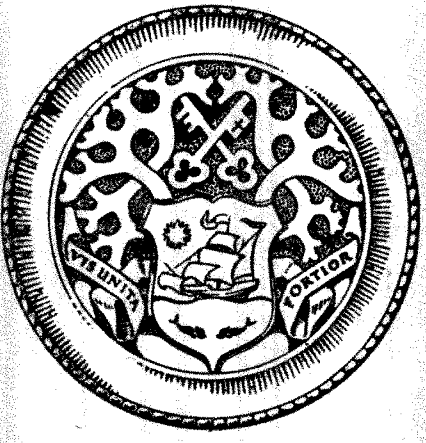

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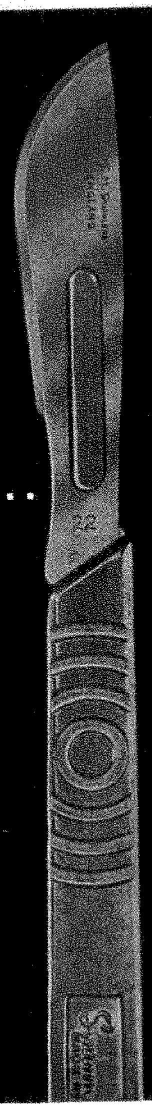

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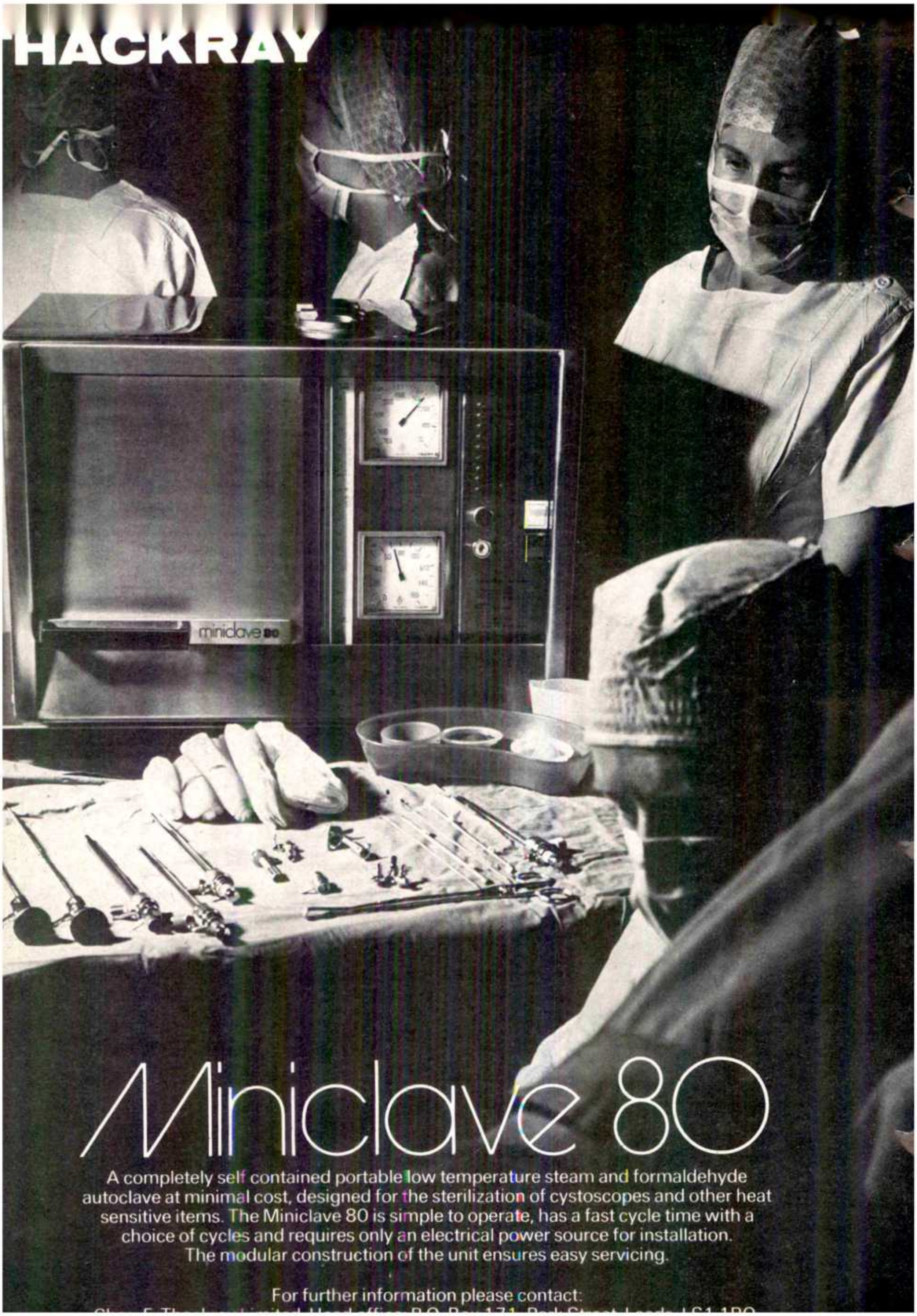

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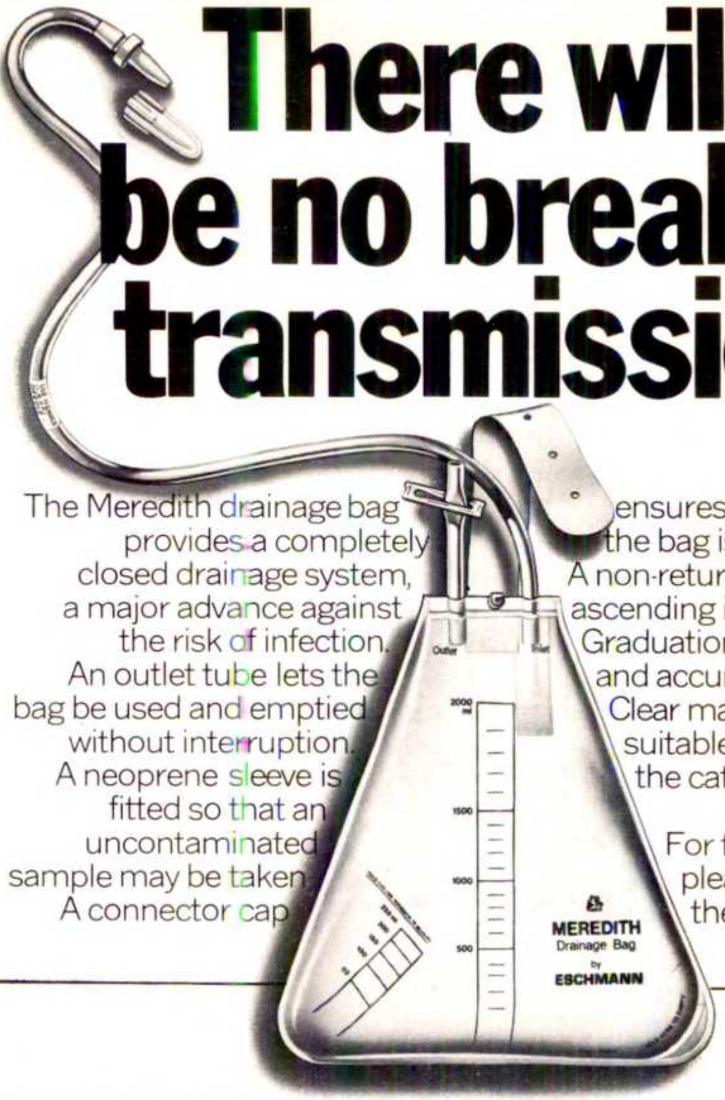

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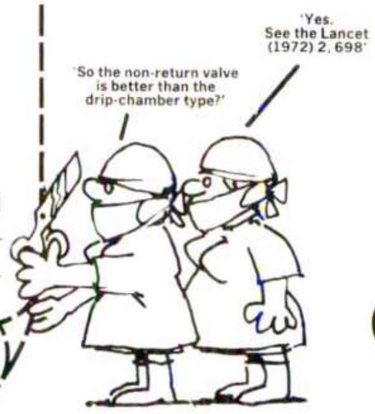
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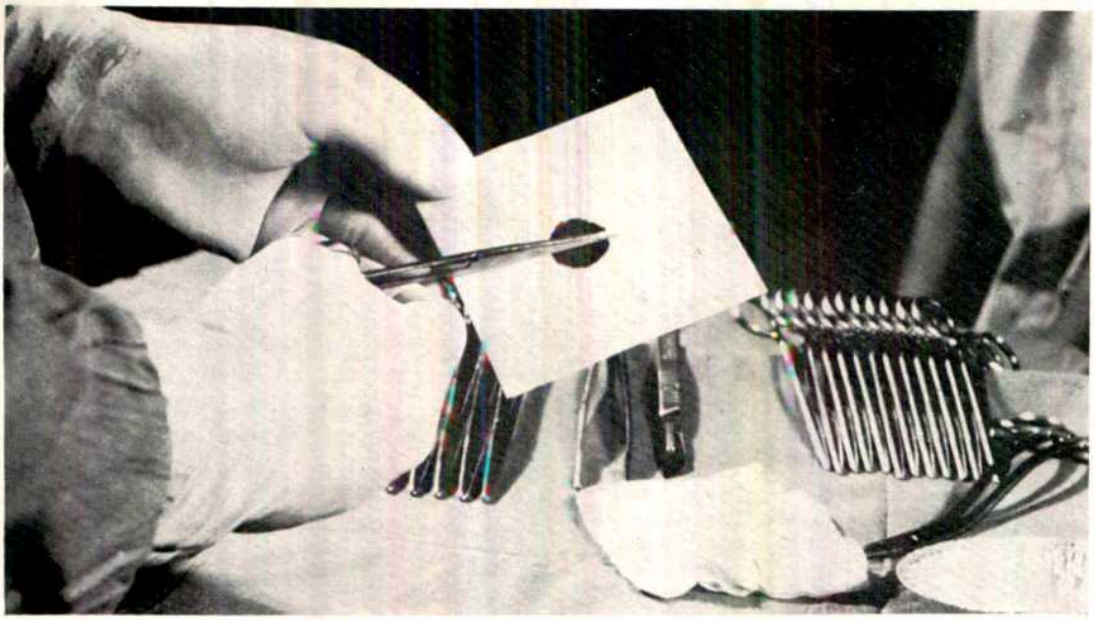

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The Role of Angiography in Diagnosis and Management of Blunt Renal Trauma

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Renal injury is suspected when trauma is followed by pain, tenderness over the kidney and haematuria. The most important investigation for the diagnosis is the intravenous pyelogram (IVP), preferably done with a high dose or infusion technique. Renal angiography has been recommended as an important complementary investigation by some authors (Olsson and Lunderquist, 1963; Vogler and Bergmann, 1963; Elkin, Chien-Hsing and Paredes 1966; Lang *et al.*, 1971; Vermillion, McLaughlin and Pfister, 1971).

Our experience with closed renal injuries is based on 223 patients who were treated in the period 1956-1973. Angiography was used as an additional investigation in 40 patients.

Patients and Methods

The patients were divided into 2 groups: those with mild and those with severe injuries (Table I). An injury was considered mild when there was no sign of shock or loin haematoma and the IVP did not show gross pathological changes. Patients with shock, loin haematoma, loss of function or gross changes such as extravasation of urine or rupture of parenchyma were considered to have a severe injury. In 23 cases there were other associated intra-abdominal injuries.

The most important investigation for diagnosis was the IVP. Retrograde pyelography and cystoscopy were used in the first years of this series.

Table I

Classification of 223 Patients with Blunt Renal Injuries

Mild	168	All managed conservatively	
Severe	55	Primary operated	30
		Conservatively managed	25

Angiography was done in 40 patients. At the beginning, it was performed on all consecutive patients but later, only in selected cases. Though it was done sometimes only a few hours after injury it proved to be a safe procedure and no complications were observed. In most cases angiography was done on the second or third day after the injury.

Technique

Angiography was done under local anaesthesia via the femoral artery. The dye was injected into the aorta and the vascular architecture of the kidneys visualised. Main stream injection has the advantage of showing accessory vessels as well as the main artery. 40 ml Urografin (76%) was

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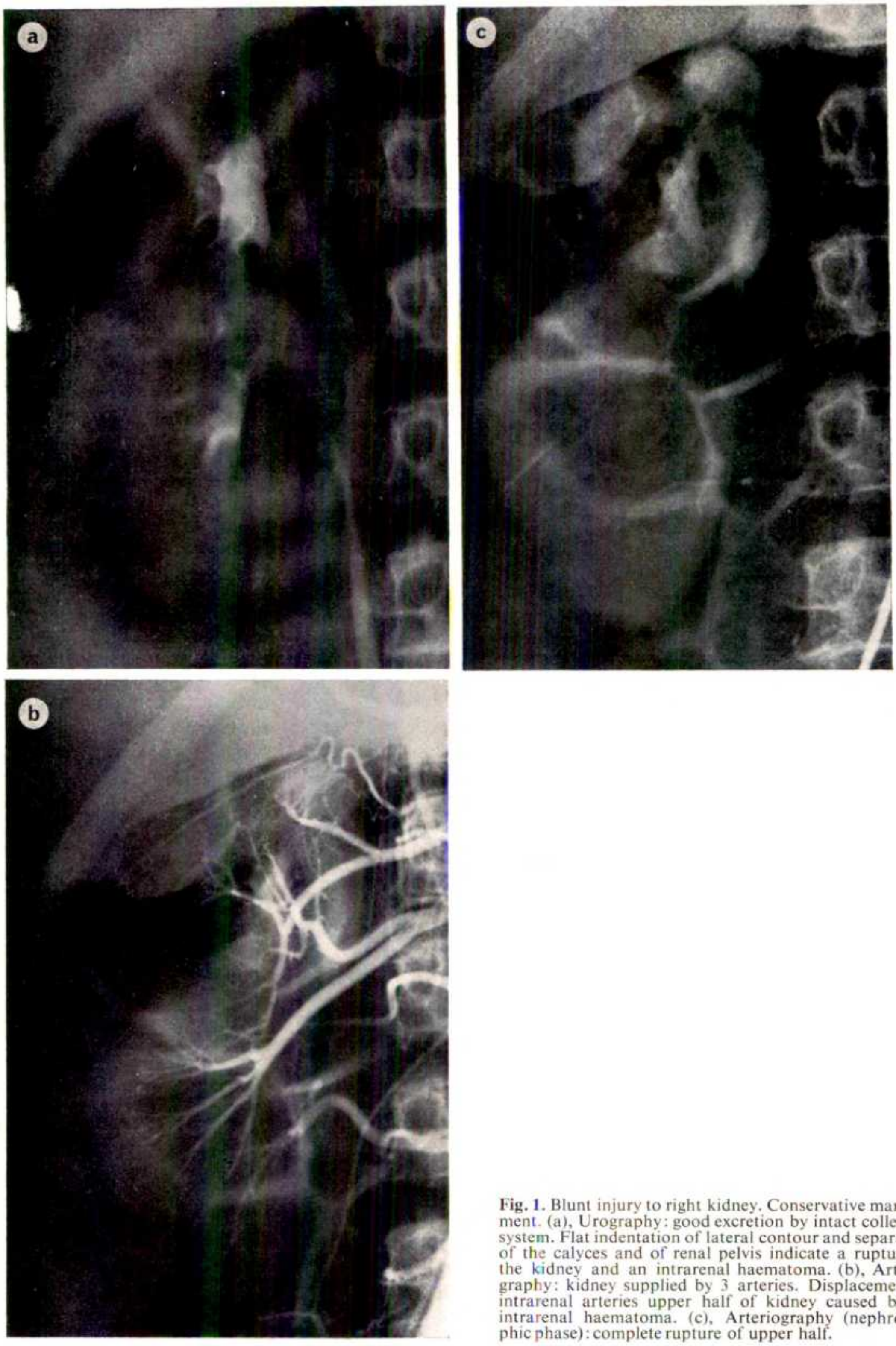

Fig. 1. Blunt injury to right kidney. Conservative management. (a), Urography: good excretion by intact collecting system. Flat indentation of lateral contour and separation of the calyces and of renal pelvis indicate a rupture of the kidney and an intrarenal haematoma. (b), Arteriography: kidney supplied by 3 arteries. Displacement of intrarenal arteries upper half of kidney caused by an intrarenal haematoma. (c), Arteriography (nephrographic phase): complete rupture of upper half.

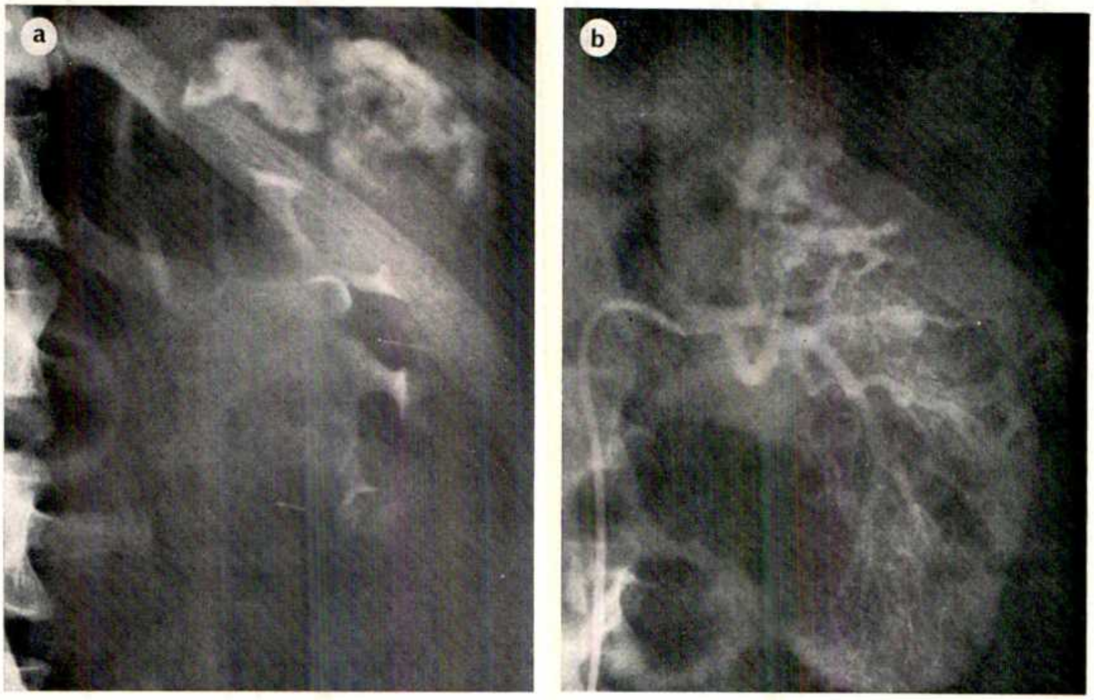

Fig. 2. Blunt injury to left kidney. Conservative management. (a), Urography showing normal excretion. Some deformity of upper calyces. Extravasation of dye from upper pole; (b), Arteriography: lack of opacification of vessels and parenchyma in upper and middle part of the kidney (necrotic parenchyma). Medial displacement of arteries at the border of this region is caused by oedema and haematoma.

given at a flow rate of 25 ml per sec. Selective renal angiography was only rarely done. It was possible to detect all vascular lesions accurately with aortography: in the nephrographic phase the parenchyma was more intensively visualised than with the IVP and ruptures were more precisely demonstrated (Figs. 1 to 4). However, in comparing the results of the IVP with the angiogram it was found that in most cases where there was an abnormality in the IVP, the angiogram also showed pathological changes. In 3 cases angiography was normal but there were pathological findings in the IVP such as delayed excretion, extravasation of urine or filling defects in the renal pelvis. The angiographic diagnosis and the management of these patients is shown in Table II.

Management

In the group with mild injuries an operation was never considered. In 1 patient from this group a nephrectomy was necessary because a renal carcinoma was revealed on the IVP and in 2 further patients a congenital hydronephrosis was found, requiring a pyeloplasty at a later date.

In the group of patients with severe injuries 30 out of 55 were explored within the first days. Because of life endangering haemorrhage 5 nephrectomies were carried out within the first hours of admission. No angiograms were done in these 5 patients. Angiograms were carried out in the 15 patients who subsequently required a partial nephrectomy. These angiograms showed either occlusion of branches of the renal artery or complete avulsion of a pole. In all but 1 of these cases major areas of parenchyma had either a diminished or no blood supply. All operations were carried out 2 to 5 days after the injury. There were no problems with bleeding and the

Table II

Angiographic Diagnosis and Management in 40 Cases

Rupture with ischaemia of major part of parenchyma	15	Partial nephrectomy Nephrectomy	14 1
Rupture with intact vascular architecture	9	Partial nephrectomy Repair and drainage Conservative	1 2 6
Intrarenal haematoma	6	Conservative	6
Normal	10	Conservative	10

Table III

Management of 55 Patients with Severe Blunt Renal Injuries

Primary operated	30	Nephrectomy Partial nephrectomy Repair and drainage	5 15 10
Primary conservative management	25	Nephrectomy (abscess) Nephrectomy (haemorrhage) Partial nephrectomy (haemorrhage)	2 1 1

Table IV

Follow-up of 50 Patients with Blunt Renal Injury

Mild injuries	19		
All conservatively managed		Hypertensive (not renal origin)	3
Severe injuries	21		
Conservatively managed	8	Hypertensive Stricture of p-u-junction Parenchymal shrinkage Calcification	6 1 6 1
Operated	13	Hypertensive Parenchymal shrinkage	4 1

necrotic parenchyma was easily identified and resected. In 1 patient in which the angiogram showed 2 deep lacerations a post-traumatic arterial thrombosis of the main artery had developed, which required nephrectomy. 10 patients required repair of a deep laceration and drainage of the perirenal haematoma; in 2 it was decided to operate after angiography, in the other 8 the decision was made on clinical signs.

The other 25 patients with severe injuries were at first managed conservatively. 2 patients were explored at 5 and 7 days after their injury because of severe haemorrhage. In 1 case a nephrectomy became necessary, in the other the haemorrhage was controlled by partial nephrectomy. A perinephric abscess due to urine extravasation occurred in 2 patients in this group and a nephrectomy was necessary in both (Table III). Angiography influenced the management in 5 patients in this group: though the IVP showed gross changes, a normal blood supply to the whole parenchyma was seen by angiography and the patients were therefore managed conservatively.

Follow-up

There were difficulties in following our patients and only 50 patients were examined 1 to 17 years after the injuries. IVP, urinalysis and blood pressures were checked. Angiography was carried out in 4 cases (Table IV).

All patients with mild injuries who were treated conservatively, had a normal IVP. 3 patients

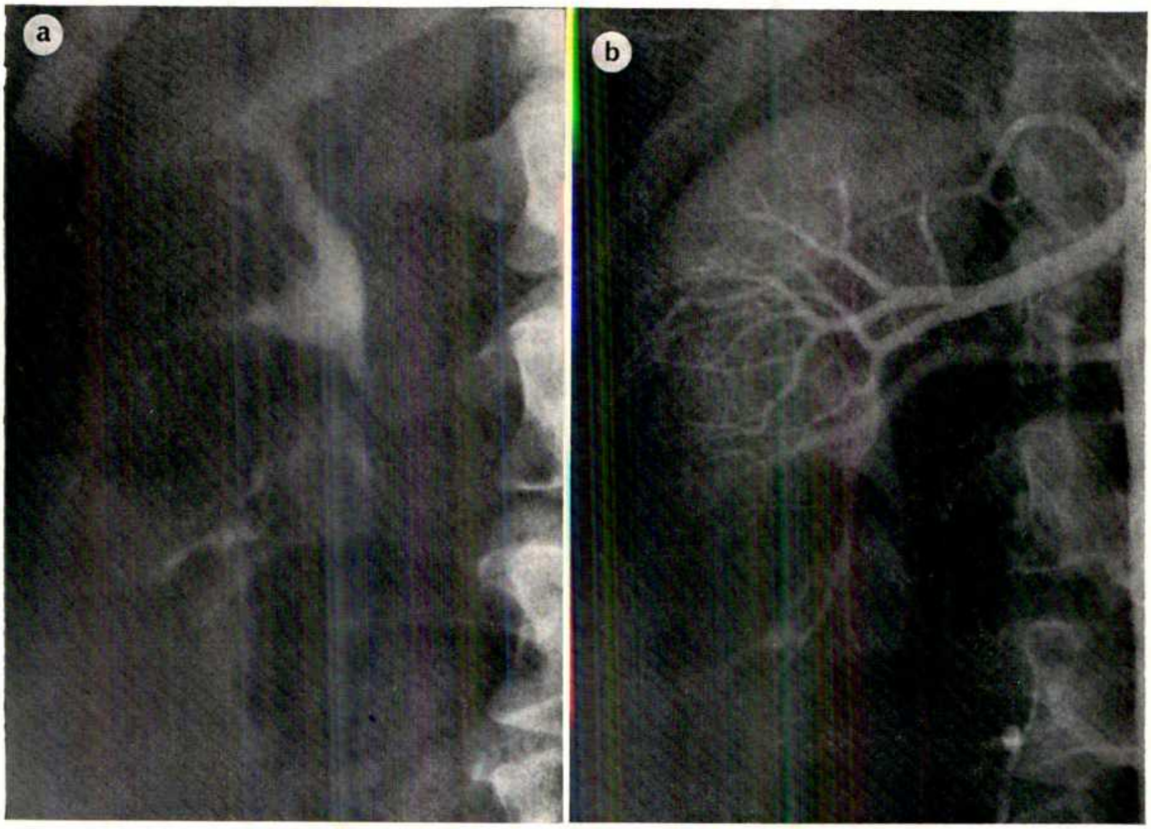

Fig. 3. Blunt injury to right kidney. Partial nephrectomy. (a), Urography: normal excretion of dye. No visualisation of the calyces of lower pole. Extravasation from lower pole. (b), Arteriography: kidney supplied by 2 arteries. Complete disruption of lower pole. Artery supplying lower pole intact. Some visualisation of parenchyma of lower pole indicated that the circulation was maintained.

had an elevated blood pressure and in 2 of them the hypertension was attributed to their age. The mild hypertension in a third, younger patient may have had another aetiology.

The highest incidence of complications was observed in the group of patients with severe injuries who had been managed conservatively. Parenchymal shrinkage was present in 6 and in 1 case a stricture of the pelvi-ureteric junction due to perinephric adhesions was found. 1 patient had calcification of the upper pole, 6 patients in this group were hypertensive: all were under the age of 30. Shrinkage of the parenchyma was found in 5 and in 3 the follow-up angiogram showed diminished vascularisation of the shrunken parenchyma. In the contracted parts of the kidneys the transport of dye was delayed. Serial angiography demonstrated this phenomenon distinctly by comparing the shrunken and the normal part of the kidney (Fig. 5). In 1 case histological examination of the removed kidney showed hypertrophy of the juxta-glomerular apparatus. In 2 the hypertension was cured by nephrectomy and in a 3rd, nephrectomy is proposed but has not yet been done. 3 hypertensive patients are not yet fully assessed.

Complications were also observed in the early operation group. The follow-up IVP showed parenchymal shrinkage in 2 cases and 4 patients had hypertension. All these hypertensive patients were young. In 1 treated by primary repair of a laceration and drainage of a haematoma, the follow-up angiogram showed diminished vascularisation at the site of the repair. Since the renin level in this patient is abnormally high a nephrectomy is planned. The 3 other patients have not yet been fully assessed.

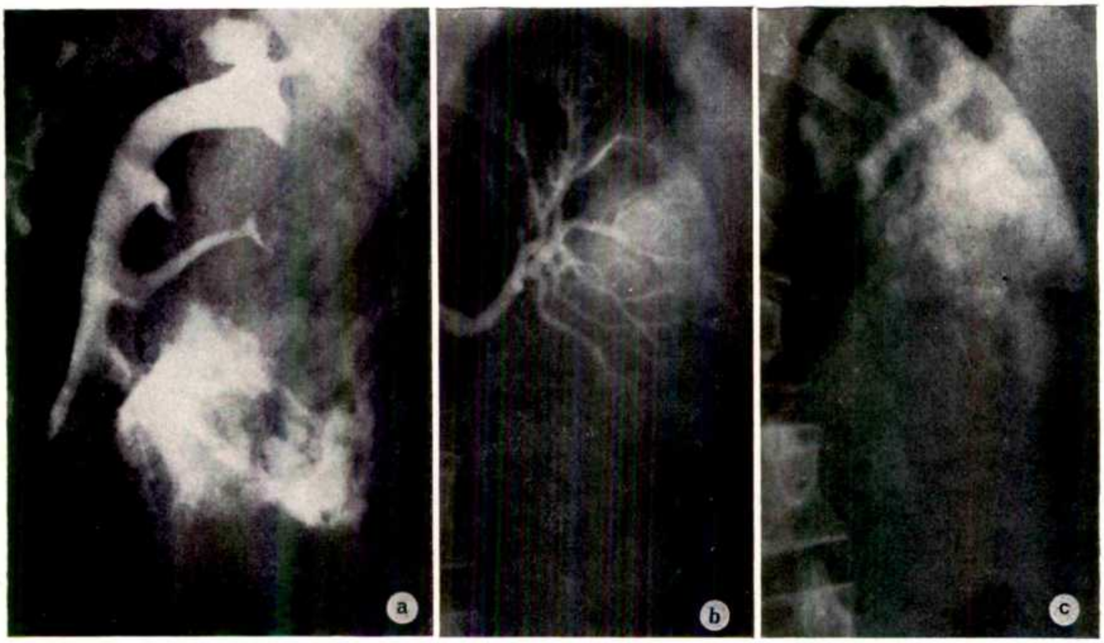

Fig. 4. Blunt injury to left kidney. Partial nephrectomy. (a), Urography showing normal excretion. Large extravasation from lower pole. (b) and (c), Arteriography: complete avulsion of the lower pole. No visualisation of lower pole artery and parenchyma.

Discussion

If a renal injury is suspected, an IVP should be performed as soon as the shock has been corrected and the blood pressure is normal. This investigation confirms the extent of the injury with an accuracy of almost 90% (Scott *et al.*, 1963; Morrow and Mendez, 1970; Lucey, Smith and Koontz, 1972) and demonstrates a normally functioning contralateral kidney. Comparisons of the IVP and angiogram show good agreement as far as the simple diagnosis of an injury is concerned. In mild injuries angiography can detect lesions which have escaped the IVP but the angiogram can show normal vascular architecture when there are pathological changes on the IVP. This has been reported by others (Elkin *et al.*, 1966; Morrow and Mendez, 1970). Angiography is the best method for demonstrating pedicle injuries, aneurysms, a-v shunts, intraparenchymal vascular disruptions and infarctions.

When should angiography be done? There is no indication for angiography in any cases of mild injury and in injuries with life endangering haemorrhage. We would recommend angiography in the severe injury which can be managed expectantly and especially if there is absence of function, large perirenal haematoma, perirenal urinary extravasation or the suspicion of a severe injury with dislocation of kidney fragments on the IVP.

In the absence of renal function it should be done as soon as possible to exclude post-traumatic thrombosis of the renal artery. When the artery is stretched during trauma, an intimal tear can occur, while the elastic media and adventitia remain intact. The intimal tear is followed by thrombosis and thrombectomy has been advocated for this complication (Ross, Ackermann and Pierce, 1970; Caponegro and Leadbetter, 1973; Fay *et al.*, 1974).

If there is function of the kidney on the IVP angiography can be performed some days after the injury. By that time any initial traumatic arterial spasm has subsided. Our indications for performing arteriography agree with those of Pryor and Williams (1975), who recommended that renal arteriography is indicated immediately if visualisation is either absent or incomplete on the IVP; an early indication is prolonged haematuria or poor visualisation on the IVP and uncertain pathology. Angiography is only justifiable if therapeutic decisions are made from the results.

The management of renal injuries is still a point of controversy. Some authors have excellent results with strictly conservative management (Slade, 1971; Ceccarelli, 1972), while others find that early surgical intervention shortens the stay in hospital and avoids post-traumatic complications (Bandhauer, 1967; Cass and Ireland, 1973). The true incidence of post-traumatic hypertension and ureteric stricture, the most dangerous complications, is difficult to evaluate because of the difficulties with long-term follow-up—a problem shared by most other authors.

We were surprised to find a relatively high incidence of hypertension in our series. Angiography should always be done in post-traumatic hypertension. If there is a post-traumatic thrombosis of a minor accessory artery the IVP can show a normal kidney while angiography clearly shows the diminished vascularisation of the parenchyma. For further assessment the renal vein renin estimation should be performed. In 4 cases of malignant hypertension the renal aetiology was well established by angiography and renal vein renin estimation. Most other series report some cases of renal hypertension (Braasch and Strom, 1943; Dowse and Kihn, 1963; Bandhauer, 1967). Lang *et al.* (1971) reported in their series that in 5 out of 13 patients who developed hypertension the arteriogram showed either a segmental infarct or a large cortical infarct without collateral supply by a capsular artery or a large perirenal haematoma. In our experience the development of hypertension could not be predicted from the angiogram. Hypertension occurred in 4 patients who had been explored: 2 of them had had a partial nephrectomy and 2 a repair of a severe laceration. However, hypertension occurs not infrequently after partial nephrectomy for other reasons (Rauchenwald, Henning and Urlesberger, 1973). Hypertension might be explained either by insufficient resection of the damaged parenchyma leaving behind parts with diminished blood supply or by thrombosis of arteries after operation.

In a period of 17 years the attitude towards the management of these cases has changed. In the first years the management was based mainly on clinical observation. Since angiography has been available we have relied on this investigation as well. Early surgical intervention can lead to nephrectomy because of uncontrolled haemorrhage (Cass and Ireland, 1973). If early surgery becomes necessary a transperitoneal approach allows good control of the renal pedicle and helps to avoid unnecessary nephrectomy. Our nephrectomy rate for all types of injuries is 4%. This is a small figure compared to other series in which the nephrectomy rate has varied from 3 to 19% (Dowse and Kihn, 1963; Bandhauer, 1967; Slade, 1971; Vermillion *et al.*, 1971; Lucey *et al.*, 1972; Pryor and Williams, 1975). We attribute our low rate to an expectant attitude of surgical treatment and the use of angiography. However, because of angiography we have performed relatively more partial nephrectomies. Although the numbers were small the highest incidence of complications occurred in that group of patients with severe injuries who were managed conservatively. We feel that there is a definite place for conservative surgery in severe renal injuries but if angiography shows an insufficient blood supply to a major part of the parenchyma we recommend removal of the necrotic tissue. Lang *et al.* (1971) have shown that a minor infarction can be managed conservatively if there is a good blood supply via the capsular arteries. Deep lacerations need not be explored if the vascular architecture of the fragments is intact. Exceptions are lacerations in which the renal pelvis is ruptured and urinary extravasation has occurred. Small intrarenal extravasations of urine and intrarenal haematomas can be managed conservatively, but one must be aware that a thrombosis of a smaller artery might ensue, leading to hypertension as in 4 cases in this series.

Conclusion

We strongly recommend an expectant attitude toward all types of blunt renal injuries and particularly, an evaluation of the extent of severe injuries by means of angiography.

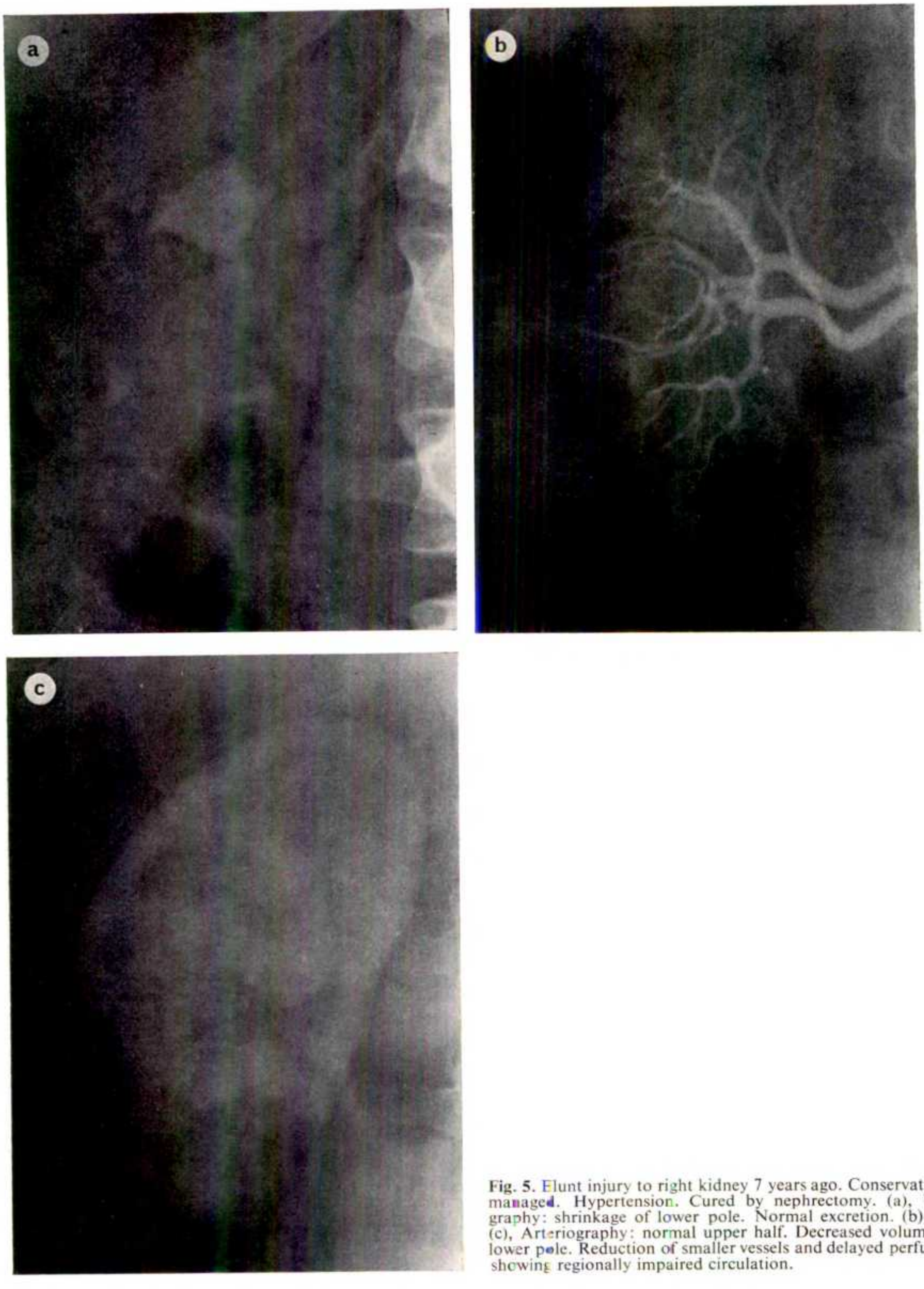

Fig. 5. Blunt injury to right kidney 7 years ago. Conservatively managed. Hypertension. Cured by nephrectomy. (a), Urography: shrinkage of lower pole. Normal excretion. (b) and (c), Arteriography: normal upper half. Decreased volume of lower pole. Reduction of smaller vessels and delayed perfusion showing regionally impaired circulation.

Summary

In a series of 223 patients with blunt renal injury, 40 patients underwent angiography. From this experience the following conclusions have been drawn:

If a renal injury is suspected the IVP must be done as soon as possible. In most cases the diagnosis can be confirmed.

Mild injuries should be managed conservatively and therefore need no angiography.

In life endangering injury there is no time for angiography. The operation should be done preferably by a transperitoneal approach to allow good control of the renal pedicle.

Patients with severe injuries should undergo angiography. If there is no function on the IVP, angiography should be done immediately to diagnose possible arterial thrombosis. In most cases angiography can be carried out some days after the trauma. This investigation provides an exact diagnosis and helps in deciding about further treatment.

If a major part of the kidney has no blood supply, or there is a rupture with a large perirenal extravasation of urine, we recommend conservative surgery to avoid early and late complications. All operations should be done some days after the trauma.

All patients with renal injuries, either operated or conservatively managed, should be carefully followed up.

Angiography should be done in all cases of post-traumatic hypertension.

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The Bristol Pyelonephritis Registry: 10 Years On

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Recurrent pyelonephritis is one of the most common diseases of the kidney. To most clinicians this term implies a syndrome of recurrent attacks of loin pain, fever and rigors, often associated with lower urinary tract symptoms of pain and frequency of micturition. It is commonly held to be a disorder of the kidney consequent upon bacterial invasion of the renal parenchyma (Beeson, 1965), yet the clinico-pathological complex of recurrent pyelonephritis may be produced by factors other than bacterial infection (Kimmelstiel, 1966; Freedman, 1967). Despite a wealth of experimental evidence (Cotran, 1969) it often remains a very difficult clinical problem with much to be desired from both diagnosis and treatment. The extent to which vascular, toxic or immunological factors are involved is not known and the description "a chronic renal disease of unknown aetiology" has been applied (Beeson, 1967) to those cases which do not meet the accepted rigid clinical and pathological criteria (Heptinstall, 1966; Freedman, 1967) of the truly bacterially induced examples of the "pyelonephritis syndrome".

280 years have elapsed since Malpighi recorded some of the detail of the renal tubules and glomeruli. It is, however, only 58 years since Lohlein (1919) gave us the first full description of the contracted, scarred kidney resulting from chronic renal inflammatory disease. An understanding of the pathogenesis of this disease which may in turn lead to its early recognition by the clinician is vital if chronic renal failure in large numbers of patients (Brunner *et al.*, 1971) is to be prevented. The spectre that constantly haunts the clinician in the patient with recurrent symptoms consistent with an inflammatory process in the urinary tract is one of progression to renal disease of severe degree, whether or not this is associated with a degree of vesico-ureteric reflux and, as we now believe, intrarenal urinary reflux at an early age (Fig. 1). It has long been held that further research into both the basic mechanisms and epidemiology of recurrent pyelonephritis holds the best hope for progress in the early diagnosis and rational therapy for this disease in the future. In an attempt to increase the understanding of the pathogenesis of recurrent pyelonephritis, a registry was established in Bristol in 1963 and this paper reports some of the findings of this prospective clinical survey.

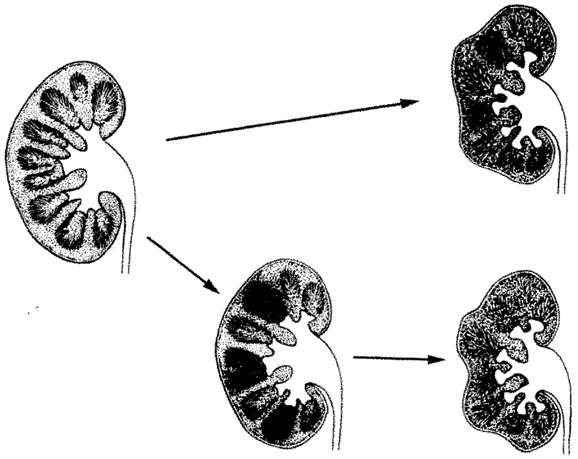

Fig. 1. Two possible pathways progressing to a scarred, contracted kidney with (below) or without (top) intrarenal reflux.

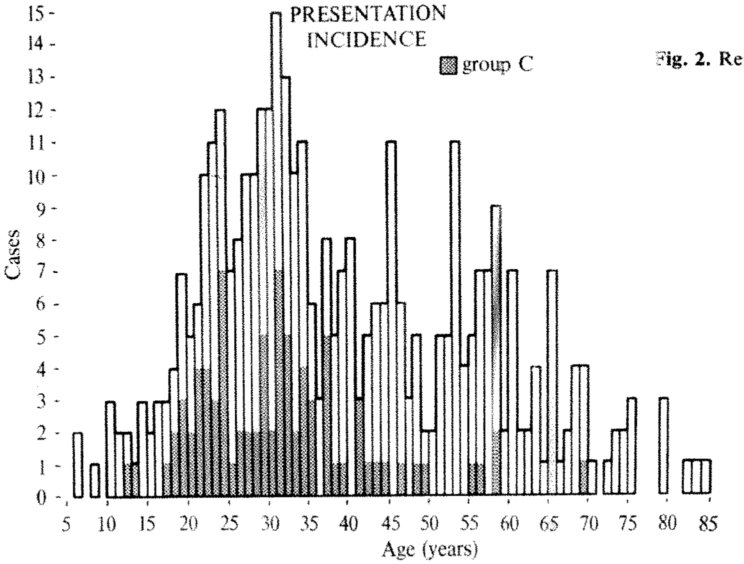

Fig. 2. Registry age distribution at presentation.

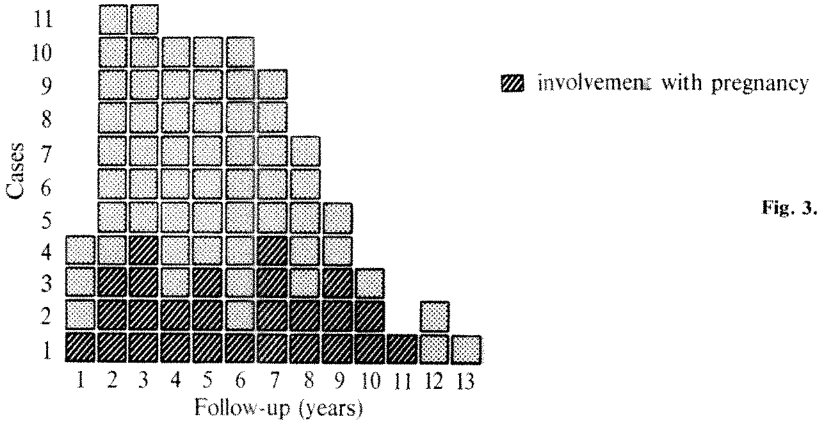

Fig. 3. Group C follow-up intervals.

Patients Investigated

The patients were divided into 3 broad groups, depending on whether the criteria for positive clinical, radiological and pathological evidence had been satisfied. In Group A were those patients in whom a strong clinical story was supported by the radiological changes of parenchymal scarring and calyceal clubbing, together with pathological demonstration of pyelonephritis in material obtained by either open or closed renal biopsy. In Group B the clinical and radiological evidence was present, but was not supported by any pathological opinion. Whilst in the third main section, Group C, those patients with symptoms consistent with a clinical diagnosis of recurrent pyelonephritis, but in whom there was no convincing radiological change and no biopsy material, were included. Relatively scant attention has been paid in the literature to the natural history of the last group of patients and the securing of suitable data was one of the primary objectives of the registry. 375 patients have been satisfactorily included in the registry, with a wide age distribution (Fig. 2). Those patients with vesico-ureteric reflux and children as a whole under the age of 5 years have been excluded for the purposes of this paper. 46% of the total

Table I

Basic Registry Structure and Case Numbers

Group		Cases
A	Positive clinical, radiological and pathological evidence	109
B	Positive clinical and radiological evidence	182
C	Positive clinical evidence only	84
	Total	375

Table II

Group C, Symptoms over Follow-up Periods

	Presentation	1 year	3 years	5 years	10 years
Loin Pain	84	41	25	7	0
Frequency	68	39	28	12	1
Pain on Micturition	63	32	23	13	1
Rigor	20	2	1	0	0
Haematuria	3	1	0	0	0
% Followed up	...	100	82	57	9

cases presented between the ages of 18 and 35 years, whereas 71% of Group C were confined to this age group (Fig. 2). It is to those Group C or "at renal risk" patients that the remainder of this paper is confined. 84 female patients, in the sexually active and child-bearing phases of their lives, with recurring and often disabling symptoms consistent with a *clinical* diagnosis of recurrent pyelonephritis, have been most carefully followed up. 48 were observed for longer than 5 years and a total of 26 patients had symptoms which were associated with a pregnancy (Fig. 3).

Symptoms

The symptom complex associated with these patients was that of loin pain, frequency and pain on micturition. The loin pain in particular was often of such severity that the patient was not infrequently admitted to hospital as an acute surgical emergency. Importantly, in nearly one-half of the cases, the loin pain *preceded* the onset of lower tract symptoms. The acute phase of the illness, however, resolved spontaneously over a 24 to 72 hour period of observation. The "free interval" between symptom episodes varied between 2½ weeks and 14 months. After 3 years less than 30% of this group were still suffering from recurrent symptoms despite an 82% follow up (Table II). As has been documented previously, the right kidney was implicated twice as often as the left side but the regression of symptoms was similar on both sides. The level of development of hypertension was not above that expected in a population sample of this age. If hypertension were present, it existed at the time of initial presentation and a precise link with a renal pathology has not been demonstrated. These findings compare markedly with the degree of hypertension present in the other 2 main groups of the Bristol Registry (A + B) which was of the order of 20%

Bacteriological Findings

Whilst it is often so difficult to achieve satisfactory urine sample collection and bacteriological analysis, every effort has been made, by careful specimen collection and the use of dip inocula where possible, to isolate an infection when suspected (Table III). There was a constant scattering of infection during the follow-up period but it must be stressed that in at least 65% of these patients there was a failure to isolate a primary infective process.

Table III

Bacteriological Findings

	Presentation	1 year	3 years	5 years	10 years
M.S.U.	84	84	68	42	3
Sterile	53	74	56	36	2
Coliform	9	2	1	1	0
E. coli	18	8	11	4	1
Other	4	0	0	1	0
% followed up	—	100	82	57	9

Table IV

Radiological Findings

	Presentation	1 year	3 years	5 years	10 years
IVP done	84	13	32	22	3
IVP normal	57	11	28	17	3
M.C.U.G. + (reflux)	13	14	0	1(1)	1
Duplex	8	0	2	2	0
Other anomaly	3	0	0	0	0
Cortical scar or calyceal deformity	0	0	0	1	0
Ureteric dilatation	16	2	2	2	0
% followed up	...	100	82	57	9

Radiological Findings

The radiological findings have been consistently satisfactory within this group (Table IV). Changes consistent with both congenital anomalies and post-pregnancy change have been noted but in only *1 case* (and that under the age of 15 years) has there been any suggestion of a progression to calyceal scarring. There was no reflux demonstrated at any stage but this could clearly have existed during the patient's early formative years. The authors feel that if the basic radiological assessment is of good quality and shows no urological lesion then repeated radiology, and more importantly *repeated irradiation*, can often be avoided.

16 of our patients passed through a pregnancy after admission to the registry. None of these women ran into a significant problem, the pregnancy progressing to its natural conclusion in each instance. Chemoprophylaxis was only used if bacterial infection had been satisfactorily demonstrated beforehand.

Discussion

The acquisition of so much negative information has surprised and pleased each of the investigators. Whilst some of the inadequacies of this survey are apparent, it has been possible to demonstrate by careful clinical follow-up that a substantial group of young, female patients, even though they suffer from recurrent and often disabling symptoms for short periods during their lives, do *not* progress to the more sinister varieties of what Professor Beeson has called, and what must remain in the light of our current evidence, a chronic renal disease of uncertain aetiology. The symptoms are notably dissociated from radiological change in the kidney and clearly run a benign course. That there are reversible changes occurring within the renal parenchyma in 25% of this difficult group of patients has been recorded by this department previously

(Davies *et al.*, 1971). Whilst the long-term studies have revealed the essentially benign nature of this problem we are unfortunately in no better position to advance a hypothesis as to the aetiology of this worrying phenomenon.

Summary

The reasons for the initiation and the basic structure of the Bristol Pyelonephritis Registry have been discussed.

The detailed follow-up data on those patients clinically at "renal risk" has been noted, with a demonstrably low incidence of proven bacterial infection, no radiological progression and minimal interference with pregnancy.

Satisfactory and reassuring information has thus accrued for the first time in a particular group of patients with often severe recurrent symptoms.

We would like to thank all our Bristol Urological colleagues for their co-operation in this survey; the Medical Illustration Department of Bristol Royal Infirmary for the graphs and figures, and Miss A. Kinghorn for the preparation of the manuscript.

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Matrix and the Infective Renal Calculus

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Mixed phosphatic renal calculi constitute 20% of most reported stone series yet the pathological consequences of the presence of these stones in the upper renal tract requires far more surgical intervention than that needed for the treatment of the more common and smaller oxalate type of calculus.

Phosphatic stones should now be recognised as a distinct disease entity for they have an entirely different aetiological nature and natural history. More importantly, the management of this type of calculus can be significantly different from that of the metabolic type of stone.

Evidence is presented to support this suggestion:

1. From an examination of the literature; and
2. From a personal study of 100 cases of surgically treated calculus disease.

Evidence from Previous Studies

It is a common experience for any surgeon who has dealt with phosphatic renal calculi to find at operation that, although the major proportion of the stone may be solid in consistency, often some, or even all, of the calculus, may be made up of a thick putty-like polysaccharide matrix substance contiguous with the calcified portion of the stone (Fig.). Such a situation is not found in relation to the pure oxalate or uric acid type of stone. Microscopic and chemical analysis (Boyce and Garvey, 1956) of these totally matrix concretions has shown that, despite their peculiar macroscopic appearance, the architectural arrangement of the matrix skeleton is entirely similar to that which exists in the fully calcified stone. In the matrix stone, however, mineralisation of the skeleton is extremely poor.

(a) Metabolic Evidence

Boyce and Stanton-King (1959) and Allen and Spence (1966) among a number of other workers, reported that when patients presenting with a purely matrix type of stone are investigated metabolically, no abnormalities of serum calcium, 24-hour calcium excretion or any of the other normally used screening tests can be detected but all values are either normal or low. The one fact that is, however, common to all patients with stones of this type is the presence of a urinary tract infection. Similarly, Thompson and Stamey (1973) have commented on the rarity of detectable metabolic abnormality in their series of 86 patients with predominantly phosphatic renal calculi and associated urinary infection.

(b) Histological Evidence

Malek and Boyce (1973) reported on the renal biopsy findings in 100 patients with and without renal calculus disease. 19% of the patients with renal stones suffered from staghorn phosphatic calculi in the major collecting system together with urinary infection but were found to have entirely normal renal biopsies. The other 81% of cases with non-phosphatic stones, however, all had biopsy evidence of "intranephronic calculosis", described by the authors as depositions of calcified PAS positive mucopolysaccharide material in the renal substance. These mixed matrix and mineral spherules have been suggested by Stanton-King and Boyce (1963) to be the nucleating precursor of the commonly occurring small oxalate stone indicating the existence of some underlying metabolic disturbance in the kidney.

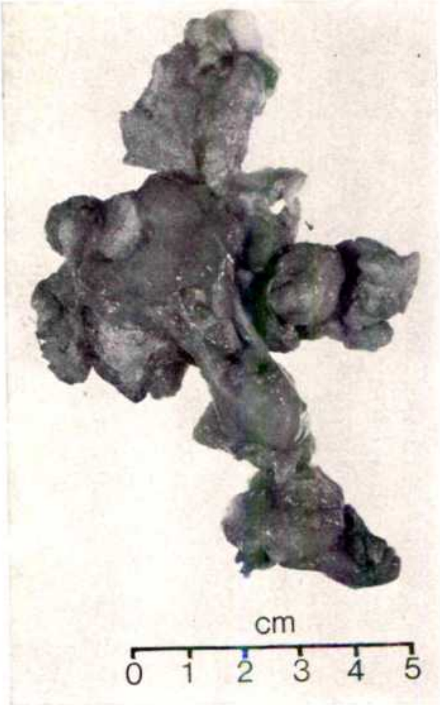

Fig. Renal stone demonstrating thick matrix material adherent to calcified areas.

Therefore, there appears to be considerable evidence that renal calculi of matrix or phosphatic type can occur in patients with no detectable metabolic abnormality either on chemical testing or on renal biopsy. Moreover, where calcium excretion is normal or more particularly low, the development of the poorly mineralised matrix calculus would strongly suggest some cause other than primary metabolic abnormality as a reason for their stone formation. The almost inevitable presence of a urinary infection with urea splitting organisms as noted by Jennis *et al* (1970), Metzner and Boyce (1971) and Thompson and Stamey (1973) would indicate that the initiating cause for calculogenesis is probably exogenous and bacterial rather than endogenous and metabolic.

Evidence from Clinical Studies

100 random and consecutive cases of upper tract calculus disease have been studied. The cases were selected only in as far as the removal of the calculi necessitated incision of the renal parenchyma and were treated by arterial occlusion and regional hypothermia, Wickham, Coe and Ward (1974). All patients underwent the normal metabolic screen of duplicate serum calcium and phosphate estimations, duplicate 24-hour urine collections for calcium and phosphate, serum uric acid, serum proteins, alkaline phosphatase and urinary spot test for cystine. The urine was cultured preoperatively, immediately postoperatively and at 1 and 3 months postoperatively. All stones removed were divided into 2 parts and one half cultured bacteriologically after washing and the other half examined biochemically.

Stone Biochemistry

Stones were routinely analysed and classified depending upon their principal mineral content. The phosphatic group of stones were classified as those stones consisting predominantly of magnesium ammonium phosphate or calcium phosphate with only occasional trace amounts of other ions. The so called "metabolic" group of stones comprised those calculi which on chemical analysis were composed of almost pure calcium oxalate, uric acid or cystine with only minute traces of mixed or calcium phosphate.

Results

100 patients were studied; 67 female and 33 male. The mean age for males was 42·2 years (range 16 to 67 years) and the mean age for females was 40·3 years (22 to 67 years).

Stone Biochemistry

The stones were allotted to the 2 main groups described above. Mixed phosphatic stones comprised 73% of the series. Metabolic stones comprised 27% of the series. The metabolic stones were divided into 16% oxalate, 9% cystine and 2% uric acid.

Infection in the Stone

Of the *phosphatic* type of stone, 79% were found to be infected on culture whilst 21% were sterile.

In contrast, only 26% of the *metabolic* type of stone were found to be infected, whilst 74% were sterile.

There is thus a marked association between infection and the incidence of phosphatic stone with a negative correlation with the metabolic stones. This relationship is statistically highly significant ($\chi^2 = 24{\cdot}82$; $P = <0{\cdot}001$).

Infection in the Urine

Of the patients with *phosphatic* stones, 70% had urinary infection before operation and 30% had a sterile urine.

Of the patients with *metabolic* calculi, 19% had a urinary infection and 81% had a sterile urine before operation.

Again there was a striking relationship between infection and phosphatic stones. This again is highly significant statistically ($\chi^2 = 21{\cdot}09$; $P = <0{\cdot}001$).

Metabolic Screen

Of the patients with *phosphatic* stones, only 19% had a detectable metabolic abnormality, usually hypercalciuria on screening, whilst 81% were adjudged metabolically normal.

Of the patients with *non-phosphatic* stones, 60% had detectable abnormality whilst 40% had no abnormality on screening.

Thus again there is a highly significant correlation between a normal metabolic assessment and phosphatic stone and an abnormal metabolic assessment and the presence of a metabolic stone. This again is statistically significant ($\chi^2 = 15{\cdot}08$; $P = 0{\cdot}001$).

The conclusion can therefore be drawn that in this series there is a highly significant positive relationship between the presence of infection in the urine and the presence of phosphatic calculus but a negative correlation with metabolic abnormality in the patient. In strong contrast is the low incidence of infection in the patient with a metabolic type of calculus but a high instance of detectable metabolic abnormality.

Discussion

The evidence presented above strongly supports the argument that the development of the phosphatic type of stone is more related to urinary tract infection than to any metabolic abnormality and represents a distinct disease entity. It is suggested that a clear definition should now be made between the so-called "metabolically induced" calcium oxalate and uric acid type of calculus and the calcium phosphate and triple phosphate type of stone that is almost invariably associated with a urinary infective process. It is also suggested that there are 2 distinct systems of calculogenesis with differing aetiologies and requiring entirely different methods of treatment. Obviously some overlap between the 2 systems can occur with secondary infection supervening upon the presence of obstructing metabolic calculi but there is much evidence to indicate the existence of 2 distinct calculogenic mechanisms.

What briefly are the 2 systems of calculogenesis and what is the evidence in support of each?

Firstly, the metabolically induced system of calculogenesis. This has already been well laid out and described by Boyce and Stanton-King in 1963 and amplified by him in more recent papers (Boyce, 1973; Malek and Boyce, 1973).

The principle steps of this scheme are:

1. Disturbed renal metabolism, *e.g.* Hypercalcaemia
Hypercalciuria
Hormonal disturbances
Circulatory disturbances
↓
2. Proximal tubular damage
↓
3. Deposition of intracellular matrix precursor
+apatite—Randall's plaques
Carr's concretions, etc.
↓
4. Intraluminal matrix substance—(? matrix substance A)
↓
5. The matrix spherule
+apatite
↓
6. Spherolith in tubules
+further mineral deposition more likely with hypercalcaemia and hyperoxaluria
↓
7. Microlith
+accretion of minerals
+absorption of mucoproteins
↓
8. *Mature Calculus* of metabolic type such as the small oxalate stone.

All stages of calculogenesis shown in the scheme above have been investigated and would appear to have been confirmed experimentally.

Secondly, the infectively induced system of calculogenesis. From the 2 sets of evidence above, there is:

1. No evidence of disturbed renal metabolism
2. No proximal tubular damage

3. No intracellular matrix precursor
4. No intratubular matrix precursor
5. No matrix spherules (Malek and Boyce, 1973)

Therefore calculogenesis starts in the *major collecting system and not in the renal substance.*

6. Normal urinary mucoproteins (Tamm-Horsfall protein)
(Urea splitters produce free NH_4
+infection— (High pH
(? bacteriologically produced mucopolysaccharide substances
polymerisation of mucoprotein
↓
7. Calculogenic matrix substance in major collecting system
+apatite
↓
8. Immature matrix calculus initially plastic to form
cast of collecting system
+time
↓
9. Mature matrix stone of staghorn type.

The evidence for each stage in this process has been examined and confirmed experimentally except for the theoretical polymerisation of the normal urinary mucoproteins by bacterial action or possibly by the ammonium ion. That such a process is biochemically feasible has, however, been demonstrated *in vitro* by Finlayson, Vermeulen and Stewart (1961) and must be considered a serious possibility in the *in vivo* situation.

If these 2 views of calculogenesis are accepted, then rational therapy for stone patients should, and often already does in practice, proceed along 2 separate and well defined pathways.

Treatment of the individual clinical stone incident is usually a problem in surgical management, but secondary follow-up treatment should be accurately determined by the aetiological nature of the individuals' calculogenic process.

Metabolic Cases. Attention should be directed to correction of their metabolic abnormality, *e.g.* hyperparathyroidism, idiopathic hypercalciuria, hyperoxaluria, hyperuricaemia, etc.

Infective Cases. Every effort should be made to rid the patient of his infection by complete removal of all infected calculi, correction of any anatomical defects in the kidney followed by adequate antibiotic therapy until the urine is sterile. From practical experience in treating large numbers of patients with urinary staghorn calculi it has consistently been found that if all infection is eradicated in the collecting system, then the vast majority of patients will remain free of calculus recurrence unless there is super-added metabolic cause for their calculogenesis (Wickham and Mathur, 1971; Wickham *et al.*, 1974).

The adoption of this or a similar system of classification would enable a more rational comparison to be made between reported stone recurrence rates from different centres. When rates of stone recurrence after surgery are reported it would seem of considerable importance to specify clearly the type of calculus under consideration. Patients suffering from a metabolic oxalate type of calculus experience a disease with a completely different natural history from that of a patient with recurrent urinary infections and secondary phosphatic concrement formation and it is of little value to make comparisons between such groups.

There are implications for the place of partial nephrectomy in the management of these renal stones. If it is accepted that phosphatic stones represent a non-parenchymal disease there is no necessity to remove large areas of renal tissue which have no relationship to calculogenesis or stone recurrence. Likewise with metabolic stones, characterised by the generalised nature of the intrarenal distribution of calcification and possible calculogenic areas, there seems no logic in removing localised areas of tissue because of possible calculogenic foci. Far more relevant is to achieve correction of areas of poor urinary drainage. From the point of view of both types of calculogenesis, partial nephrectomy would seem to be an unnecessary procedure.

Summary

From the basis of an examination of the literature, and on a personal exerience of the surgical treatment of 100 cases of calculus disease, the suggestion is made that 2 distinct mechanisms of calculogenesis should be recognised. Calculi of metabolic origin should be considered as having an entirely distinct aetiological mechanism. Phosphatic calculi are apparently determined by the existence of urinary tract infection. Partial nephrectomy does not seem indicated for either type of disease.

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Uromucoid Excretion of Normal Individuals and Stone Formers

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Uromucoid and Tamm-Horsfall glycoprotein which are of similar structure have been found, by immunological methods, in the matrix of a variety of kidney stones (Fletcher, 1972). Because of this, the excretion of protein in the urine of patients with calculus disease of the kidneys has been measured and Boyce and Swanson (1955) found an increased amount of uromucoid. According to their results and the investigations of others (Dulce, 1958) a quantitative interdependence of uromucoid and the genesis of stones was established. A connection with the theory of matrix of stones seemed to be evident.

At that time only the method of salt precipitation was available for measuring uromucoid and the examination of a large number of patients was difficult because of this complicated and not sufficiently exact method of determination. We have developed a quantitative immunoassay for human uromucoid (Bichler, Haupt, Uhlemann and Schwick, 1973) and we now report our experience in measuring uromucoid excretion in normal individuals and in stone formers.

Patients and Methods

Urine samples (24 hours) were collected from 17 female and 32 male normal subjects. In 6 male normal subjects, in the age range of 20 to 27 years, the uromucoid excretion was analysed over a period of 24 hours at 7-hour intervals to determine a possible circadian rhythm.

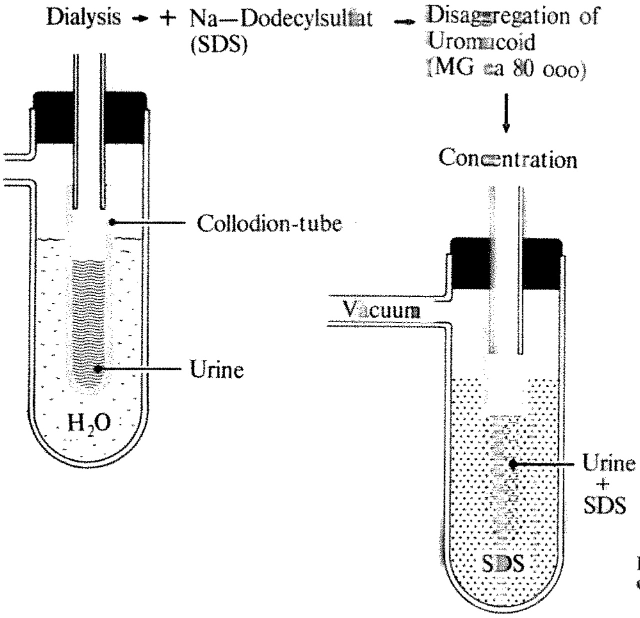
Dialysis → + Na—Dodecylsulfat (SDS) → Disaggregation of Uromucoid (MG ca 80 000)
Concentration
Collodion-tube
Urine
H_2O
Vacuum
Urine + SDS
SDS

Fig. 1. Preparation of urine for the determination of uromucoid.

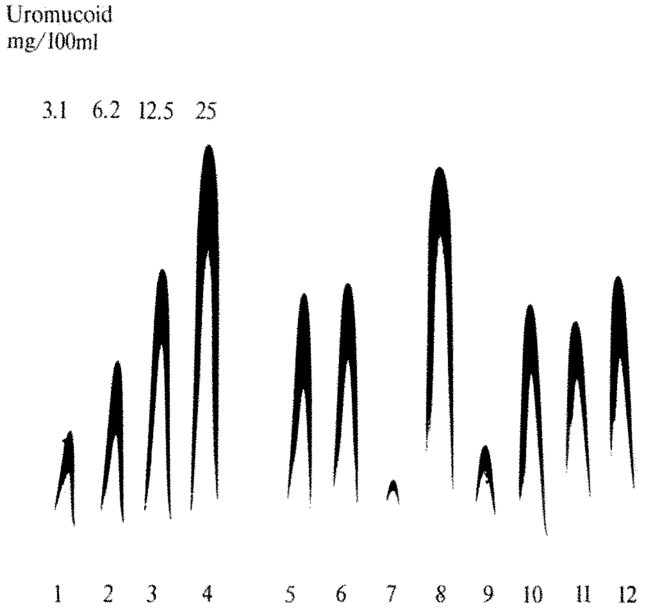

Fig. 2. Electroimmunoassay by the Laurell technique.

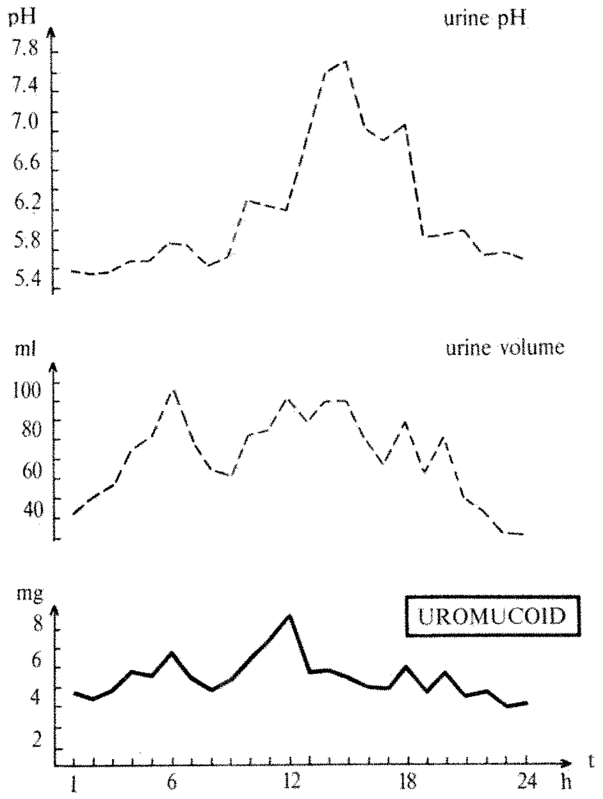

Fig. 3. Uromucoid, urine pH and urine volumes in normal subjects (n = 12) during the 24 hours.

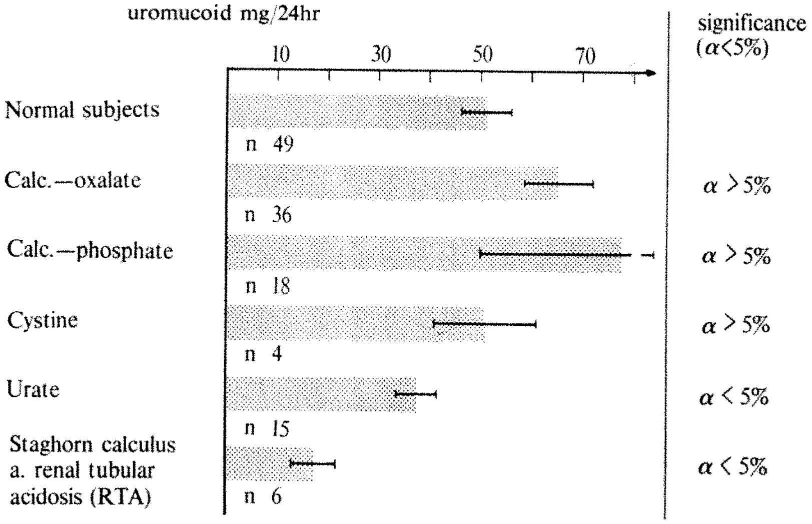

Fig. 4. Excretion rate of uromucoid in normal subjects and stone formers (mg/24 hours).

The quantitative assessment of uromucoid was carried out in 79 patients with stones; only the urine of patients whose stone had been analysed was examined.

Electroimmunodiffusion was used for the immunological determination of uromucoid in the urine (Laurell, 1966). In preparation for this, urine samples (5 ml of a 24-hour urine) were dialysed to remove the electrolytes, especially potassium (Fig. 1). In order to disaggregate the highly molecular uromucoid, sodium dodecyl sulphate (SDS) was added to the urine and then concentrated (Bichler *et al.*, 1973).

Linear calibration curves were obtained after plotting the lengths of the Laurell "rockets" versus the standard concentrations (Fig. 2). Localisation of uromucoid in the human kidney was carried out by immune histological technique with a fluorescein isothiocyanate (FITC) conjugated antihumanuromucoid globulin.

Results

The average excretion rate of human uromucoid was found to be 55·9 ± 6·2 for male and 42·2 ± 8·2 mg/24 hours for female adults. These results are in accordance with those of Grant and Neuberger (1973). Figure 3 shows the uromucoid excretion over a period of 24 hours measured at hourly intervals in comparison to the urine volume and the urine pH. There is no clear evidence that uromucoid is washed out passively by the urine flow or is actively secreted by a circadian rhythm of the tubular cell.

However, the acidity of urine clearly follows the circadian rhythm of the tubular cell as a parameter of the tubular function: a higher H^+ ion concentration in the urine occurs during the night compared to the day (Mertz, 1964).

The uromucoid excretion of stone patients is shown in Figure 4. In patients with calcium oxalate, calcium phosphate and cystine stones no significant change in comparison to normal individuals could be found, but patients with urate stones showed a significant decrease of the uromucoid excretion rate. Patients with renal tubular acidosis (RTA) and extensive stone development showed a significant decrease of the uromucoid excretion rate (Table).

Figure 5 shows a section of the human kidney tissue after an immunoincubation with FITC conjugated antihumanuromucoid globulin. The cells of the distal and collecting tubules clearly

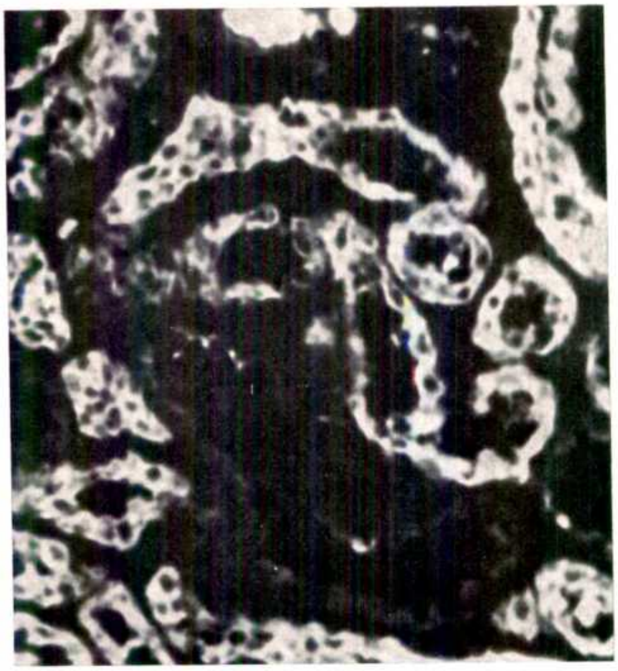

Fig. 5. Localisation of uromucoid in the human kidney (tubule cells) by immune histological technique with a FITC conjugated antihumanuromucoid globulin.

show fluorescence, indicating that these cells synthesise uromucoid. It follows that the tubular cell contains uromucoid and that this is where the uromucoid is formed. Our investigations support the opinion of McKenzie and McQueen (1969) that uromucoid is formed in the distal tubule.

Discussion

Our results in patients with calculus disease differ from the results of Boyce and Swanson (1955) and Dulce (1958), who found an increased uromucoid excretion rate. We found no simple quantitative relation between the uromucoid excretion rate in the urine and the genesis of stones.

A significant decrease of the uromucoid excretion rate in patients with renal tubular acidosis and extensive stone formation was of pathophysiological interest. Nephrolithiasis and nephrocalcinosis occur in 73% of all patients with renal tubular acidosis (Marquardt. 1973). These may be caused, in part, by a relatively high urine pH, as a result of which, calcium becomes insoluble. All of our patients were unable to acidify urine when given an acid load.

The importance of the decrease of uromucoid is not yet clear. The decrease is probably the result of destructive changes in the tubular epithelium, usually as a result of pyelonephritis. The significant decrease in uromucoid excretion rate in patients with urate stones can be assumed to be the result of a defect in tubular epithelium.

The physiological function of uromucoid is not clear. Because of its chemical structure as a mucoprotein it may have a protective effect for the tubular cells, comparable to the effect of mucin in the stomach. Uromucoid may also have a function in the transport of electrolytes and H^+ ions across membranes.

Table

Uromucoid Excretion Rate in Patients with Staghorn Calculus and Renal Tubular Acidosis (RTA)

No.	Pat.	Age Sex	Uromucoid (mg/24h)	Acid load (a.l.) NH_4Cl 0·1 g/kg p.o. pH (init. value)	 pH (after a.l.)	Base-Exc. mEq/l
1	R. R.	44 ♂	25·0	7·62	6·39	−0·7 mEq/l
2	H. E.	65 ♀	0	6·38	6·30	±0 mEq/l
3	K. F.	54 ♀	26·4	6·45	6·05	−1 mEq/l
4	K. J.	45 ♀	2·6	6·35	6·20	−7·2 mEq/l
5	S. V.	73 ♀	7·4	8·35	7·85	+1 mEq/l
6	M. M.	49 ♀	7·0	6·90	6·04	−1·9 mEq/l

Summary

Uromucoid excretion was measured in 49 normal subjects and 79 patients with stones.

The results showed no significant differences in the uromucoid excretion rate between these 2 groups; there was no simple quantitative relationship between uromucoid excretion rate and the genesis of stones.

It is suggested that uromucoid may be concerned in a protective function of tubular epithelium and also in the transport of electrolytes and hydrogen ions.

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Childhood Urolithiasis in the United Kingdom and Eire

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Lett, in 1936, showed that endemic calculus disease in children ceased to be a problem in England by about 1920. The endemic calculus was characterised by a predominance of uric acid bladder stones with sterile urine. This disease is also disappearing from many countries around the Mediterrranean where it was once very common, for instance in Sicily and the Lebanon (Anderson, 1969). Factors leading to the disappearance of endemic stone disease are related to improved nutritional standards, especially the introduction of a mixed diet rather than one predominantly dependent upon cereal products.

In the United Kingdom and parts of Europe infants tend to have infected mixed phosphate, upper tract stones; yet this type of disease is rare in North America (Thomson, Ross and McCoy, 1967) and in Scandinavia (Andersen, 1968). In recent years there appears to have been an increase in the incidence of upper urinary tract calculi in young children associated with *Proteus* urinary tract infection. We have reported 120 children with urinary calculi referred to the Hospital for Sick Children, Great Ormond Street and Shaftesbury Hospital, London, between 1966 and 1971 (Ghazali, Barratt and Williams, 1973). This rising incidence of upper urinary tract calculi has also been seen in the Bristol area (Gaches *et al.*, 1975).

In order to ascertain the magnitude of the clinical problem, consultant urologists and paediatric surgeons in the United Kingdom and Eire were sent a postal questionnaire requesting details of children with urolithiasis treated in 1972 and 1973. Information on the age, sex, site and presence of *Proteus* infection was sought. The findings of this study are described in this communication. Also included in the discussion are observations not previously reported on reflux and calculi remnants as aetiological factors in the genesis of these calculi. This study was part of the earlier series.

Incidence

87%of the 430 surgeons circularised replied to the questionnaire. 152 children were operated on during the 2-year period 1972-73. The age of the children at presentation is shown in Fig. 1. Similar data from earlier studies (Williams and Eckstein, 1968; Ghazali, Barratt and Williams, 1973) are included for comparison. These show that there is little difference in the age distribution between the three series. 65% of the children were under 5 years of age.

Of the 152 cases, 103 were male and 49 were female; the male preponderance is particularly evident in early life.

Distribution

No particular stone region was identified from this study of the United Kingdom and Eire. Most stones were seen and treated in London and Liverpool because of referral to paediatric urological centres.

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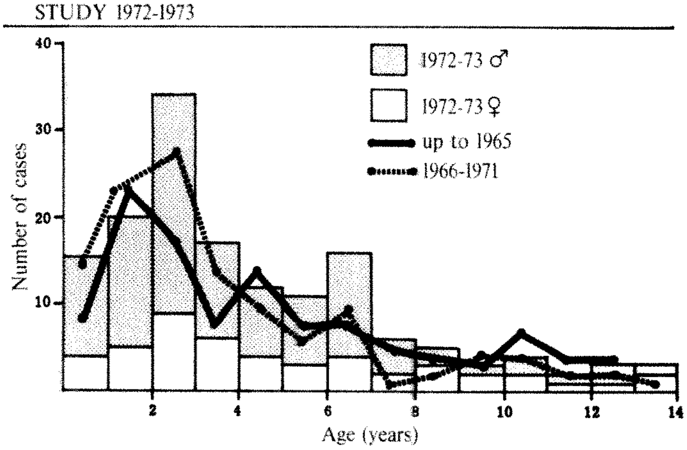

Fig. 1. Age of children at operation for urinary lithiasis. Similar data from earlier studies (Williams and Eckstein, 1968; Ghazali, Barratt and Williams, 1973) are included for comparison.

Site

127 had calculi in the upper urinary tract and in 16 children the stones were confined to the bladder. Of the children with upper tract calculi, 8 also had bladder involvement, 10 were confined to the ureter, 109 to the kidney and 8 had stones in both kidney and ureter. 25 of the calculi were bilateral, and of the unilateral upper tract calculi, 65 were left-sided and 35 right-sided. 1 child had a stone impacted in his urethra. This pattern of upper tract involvement strongly contrasts with the classical form of endemic stone disease in childhood.

Infection

In 124 children the urine was infected on admission to hospital (Fig. 2). 87 of these, particularly the younger children, were infected with a *Proteus* species and this group largely accounted for the peak of incidence in the first few years of life. The age at presentation of children with infections other than *Proteus* (predominantly *Esch. coli*) or with sterile urine was more evenly distributed throughout childhood. The ratio of infected stones (*Proteus* and *Esch. coli*) to sterile stones was about 5 to 1. This incidence is similar to that reported in the earlier series.

Discussion

The data presented indicate that childhood urolithiasis remains a substantial clinical problem. A definitive causative factor appears to be urinary infection with a *Proteus* organism. This organism is relatively rare in uncomplicated urinary infections in childhood. Hence, there must be some other as yet unidentified factor which causes an infant during the first few years of life to form a stone when infected with a *Proteus* organism. Observations in the present series were very similar to those previously reported (Ghazali, Barratt and Williams, 1973). Four-fifths of these children were male and in 90% the upper urinary tract was involved. The children were from all social classes in the population and from several immigrant groups but no negro child was found to have calculus disease. This relative immunity of negroes to urolithiasis has been previously noted.

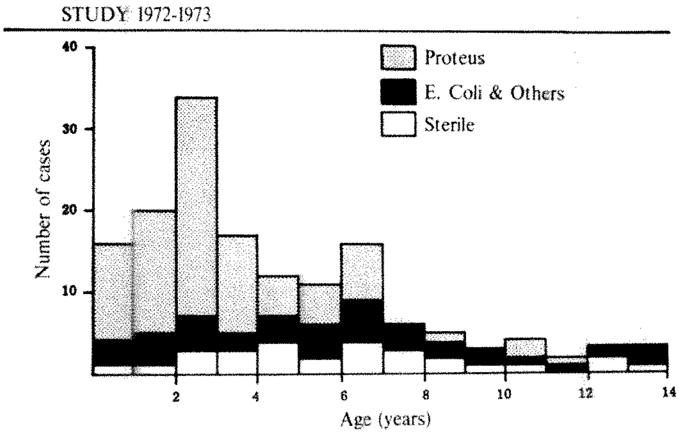

Fig. 2. The incidence of *Proteus* and other infections in children with urolithiasis.

Underlying urological malformations recognised were severe ureteric reflux, pelvi-ureteric junction obstruction, abnormalities of fusion or rotation, neurogenic bladder and epispadias. Analysis of the urine cultures revealed that the majority of these children, particularly the younger age group, were infected with a *Proteus* species and this group largely accounted for the peak of incidence in the first few years of life. Subsequently we found thet even if the urine contains *Esch. coli* organisms it may well be possible to culture *Proteus* organisms from swabbing the cut kidney surface or stone.

The major identifiable factor in calculi recurrence following surgical removal appeared to be the persistence of *Proteus* infection. No child had a recurrence a second time. The calculi which form in infected urine due to *Proteus* organisms consist of organic matrix in which is deposited struvite (magnesium ammonium phosphate) and apatite (basic calcium phosphate).

The principal aetiological factor in the genesis of these calculi is the urease activity of the *Proteus* organism: the high ammonium ion concentration leads to the precipitation of struvite and, by raising the pH, favours the precipitation of apatite. The effect of alteration of calcium concentration on this system is marginal (Robertson and Nordin, 1969).

Table I

Reflux in Children with Urinary Calculi: 120 Patients

98 cystograms available for analysis

56 cystograms performed *before operation*:
- 20 reflux present
- 18 postoperative check cystograms
  - 8 continued to reflux
  - 3 required reflux prevention operation

42 cystograms performed *after operation*:
- 9 reflux present
- 8 check cystograms
- 4 continued to reflux
- 2 required reflux prevention operation

Table II

Calculi Remnants: 120 Children with Urinary Tract Calculi

101 Pre- and postoperative X-rays 98 Check X-rays at operation	Available for assessment

Results

- 12 had calcified flakes visible on last X-ray taken during operation
- 16 visible calculi on postoperative follow-up X-rays:
  - 4 have passed the calculus
  - 12 have solitary residual calculus with no signs and symptoms

A survey of urine calcium excretion in the 120 children previously reported showed that hypercalciuria defined as greater than 6 mg/kg/24 hours (Royer, 1961) was present in 10% of children. The relevance of the observation of hypercalciuria in a few of these children is unclear. Indeed, it is difficult to understand the role of hypercalciuria in a system in which the main crystal constituent is struvite (magnesium ammonium phosphate). However, in all the stones that have been analysed by X-ray diffraction crystallography, it has been found that as well as struvite they contain apatite which is basic calcium phosphate. This factor emphasises the multifactorial aetiology prevalent in the genesis of these calculi.

Not all children with urinary calculi had ureteric reflux. Dilatation of the lumbar part of the ureter is frequently seen on intravenous urography. It has been postulated that this dilatation may be the result of chemical toxins liberated by the *Proteus* organism. 98 micturating cysto-urethrograms were available for analysis in the 120 patients in the previous series (Table I). Of these, 56 cystograms had been performed prior to surgery. Reflux was present in 20 and persisted in 8 postoperative micturating cysto-urethrograms. 3 required surgery to prevent reflux. 42 children had micturating cysto-urethrograms performed after surgery, Reflux, as expected, was present in only 9 and of these 2 required reflux-prevention procedures. Hence, not all children with stones reflux and of those who do, only a minority require surgical procedures to correct it.

Stone remnants have not appeared to be a problem, *i.e.* as a nidus for further stone formation. This is shown in Table II. Of the 120 children with urinary tract calculi, 101 had pre- and post-operative X-rays available for assessment. 98 of these patients had had check X-rays at the time of the operative procedure. 12 demonstrated calcified flakes visible on the last X-ray taken during the operation. In the follow-up period the number with visible calculi had increased to 16. Of these, 4 children have passed the calculus spontaneously and in 12 solitary residual calculus is present. These children are symptom-free.

Studies were undertaken to elucidate the role played by hypercalciuria and *Proteus* infection in the genesis of these calculi. The calciuretic response to a milk load was investigated on the hypothesis that the peak urine calcium concentration might be an important factor in stone formation. This was looked at partly because lactose is a known stimulant for calcium absorption and partly because the peak age of incidence of diagnosis of urinary calculi coincides with the peak milk consumption. All the stone-formers had a higher urine calcium concentration than the healthy children in response to the milk load but some children with urinary infection but without stone had a similar response of calcium excretion to stone formers. The role of *Proteus* organism was examined by studying all the children who were seen at the Hospital for Sick Children in 1973 who were shown to have unequivocal *Proteus* infections (Ghazali, Barratt and Williams, in preparation). Of the children with *Proteus* urinary infection, less than a quarter had stone. The only function which discriminated between stone-formers and non-stone-formers was the higher colony count in the former group.

The infected calculi seen in the United Kingdom and Eire have a peak age incidence in the 2nd and 3rd years of life. This is in common with the classical endemic calculi. Also the low recurrence rate; but in contrast, upper tract stones are seen much more frequently. No definite stone areas were identified. We have not been able to explain the difference between the incidence of stone in the United Kingdom and Eire in comparison to that observed in North America and Scandinavia.

Summary

152 children with urinary calculi were treated in the United Kingdom and Eire in the years 1972 and 1973.

There was a marked male preponderance particularly evident in early life.

In 124 children the urine was infected on admission to hospital; in 87, particularly the younger children, this was with the *Proteus* species. Awareness of the relationship between *Proteus* urinary infection and matrix calculi is stressed.

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Stone Screening and Follow-up are Necessary?

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The occurrence of urinary tract stones and their location has a characteristic geographical distribution. Bladder stones are endemic in many areas of Africa, India and Pakistan and tend to disappear in areas with technological progress and rising standards of living. The majority of these stones consist of ammonium acid urate (Sutor, Wooley and Illingsworth, 1974).

In contrast, in Europe and the USA, with a higher standard of living, calcium-containing stones of the upper urinary tract predominate (Prien and Prien, 1968). These stones are frequently associated with a metabolic disorder which if left untreated may lead to a recurrence of the stone with its attendant infection and impairment of renal function.

The frequency of recurrence is variable, some authors reporting that 85 to 90% of patients suffer from solitary stones (Baker and Connolly, 1956; Garvey and Boyce, 1956), whereas Williams (1968) found that 75% of patients with a urinary stone will form another. When a specific metabolic disorder associated with renal stones, *e.g.*, idiopathic hypercalciuria or renal tubular acidosis, can be identified and treatment of that disorder instituted, then a significant reduction of stone recurrence has been reported (Yendt, Guay and Garcia, 1970; Murphy, 1972).

This paper is part of a long-term survey undertaken to determine:

(*a*) the incidence of metabolic abnormalities in patients with renal stones,
(*b*) the incidence of stone recurrence in patients with a metabolic disorder not medically treated,
(*c*) the necessity to follow-up these patients,
(*d*) whether there is any point in offering these patients with a metabolic abnormality medical treatment with the attendant side-effects.

Patients and Methods

120 patients who had passed a stone or had unequivocal radiological evidence of a stone underwent detailed metabolic studies. 72 men and 48 women, ages ranging from 19 to 78 years with a mean 45 years have been followed-up for a mean period of 5 years (range 6 months to 12 years).

During this period many more patients with stones were seen but did not have a completed series of metabolic investigations. As it was not possible to determine fully the presence or absence of a metabolic abnormality in these patients, they have not been considered. There is nothing, however, to suggest that this series is highly selected. The incidence of first time and recurrent stone formers is similar in both groups. Only those patients who had all of the investigations completed have been included (Table I).

Results and Follow-up

When infection was present this was considered secondary to the stone and only when infection was present without a metabolic abnormality was it considered the primary cause of the stone.

The metabolic abnormalities detected are shown in Table II.

Table I

Metabolic Investigations

Investigation	Frequency	Range
Fasting serum Ca^{++} No venous compression	×2	9·0 to 10·6 mg%. Corrected to serum albumin 4·6 g% (Berry *et al.*, 1973)
24-hr urine Ca^{++} excretion Normal diet	×2	Males 350 mg/24 hr Females 250 mg/24 hr
Serum uric acid	×2	7·5 mg%
Urine acidification test (Wrong and Davies, 1959)	×1	Urine pH 5·6 after 6 hr
Urine amino-acid chromatography	×1	No cystine
Urine culture	×2	

Table II

Results of Metabolic Studies

Abnormality	No.	Male	Female	Incidence
Idiopathic hypercalciuria	37	26	11	31%
R.T.A.	23+2*	16	7+2*	21%
1° Hyperparathyroidism	4	2	2	3%
Cystinuria	3	1	2	2·5%
Uric Acid	3	3	—	2·5%
Infection	12	2	10	10%
No abnormality	35	22	13	29%

* 2 cases of complete R.T.A. 23 cases incomplete R.T.A.

16 patients were found to have multiple abnormalities—9 with idiopathic hypercalciuria, 4 with primary hyperparathyroidism and 3 with cystinuria were unable to acidify their urine.

In assessing what happened to each kidney containing a stone(s), 3 possibilities have been considered:

1. the stone was passed,
2. the stone was removed either (*a*) completely or (*b*) incompletely,
3. the stone was left *in situ*.

In Tables III to V the results are expressed as a change or no change. This is to say with no change no further stones have been passed or produced or when a stone was incompletely removed or deliberately left *in situ*, then it has not significantly changed in size.

The results of follow-up in those patients with normal results are shown in Table III.

The results in those patients with abnormal metabolic investigations are shown in Tables IV and V.

Table III

Normal Investigations, 35 patients

		No change	Change	Av. follow-up
Stone passed	11	4	...	1·5 yr
		...	7	3 yr
Stone removed				
No. of kidneys	13			
Complete	9	8	1	3 yr
Incomplete	4	2	2	4 yr
Stones left *in situ*	15	...	2	9 yr
		13	...	3·5 yr

Table IV

Idiopathic Hypercalciuria 37 patients

		No Change	Change	Follow-up
Stone passed	14	2	...	2 yr
		...	12	7 yr
Stone removed				
No. of kidneys	17			
Complete	13	5	8	5 yr
Incomplete	4	...	4	4 yr
Stone left *in situ*	6	...	2*	5·5 yr
		4	...	2 yr

* Nephrectomy required

In the 4 patients with primary hyperparathyroidism there has been no significant change in the renal calculi or calcification over the mean 2-year follow-up after removal of their parathyroid adenoma. Of the 3 patients with a raised uric acid 1 has produced a further stone in spite of medical treatment, though there is doubt as to whether he was consistent in taking his therapy. 1 patient with cystinuria has developed chronic renal failure and requires dialysis. The 2 other patients have progressive renal impairment as a result of their stones, despite medical treatment.

Discussion

In this series of 120 patients, 60% were found to have a treatable metabolic abnormality.

Only 20% of these patients were first-time stone formers. The remainder had recurrent stones.

The finding of idiopathic hypercalciuria in 31% of the patients studied is similar to that of other series. Powis *et al.* (1974) reported an incidence of 32·5% in recurrent stone formers. Melick and Henneman (1958) reported 32% and Rose and Harrison (1974), in a highly selected series, reported 66%. A similar incidence of hyperparathyroidism, cystinuria and raised uric acid has been found by these authors.

Table V

Renal Tubular Acidosis 25 patients

		No Change	Change	Av. follow-up
Stone passed	13	1	...	3 yr
		...	12	4·5 yr
Stone removed				
No. of kidneys	8			
Complete	1	1	...	1 yr
Incomplete	7	...	7	6 yr
Stones left *in situ*	3	...	2	3 yr
		1	...	2 yr

However, a comparative incidence for renal tubular acidosis either of the complete or incomplete form is difficult to find in the urological literature. In this study the lower limit for the normal response to acidification has been taken as 5·6. Most authors would accept a lower limit of 5·3 in normal patients. However, in the first 2 years of this study, urine pH was measured with pH papers. A level of 5·6 has been taken to overcome any minor inaccuracies which may have occurred. Urine pH has been measured for the last 4 years using a pH meter. Cochran *et al.* (1968) compared 24 patients with renal stones who had the incomplete form of R.T.A., *i.e.*, were unable to acidify their urine after an ammonium chloride load but who had no systemic acidosis with its sequelae, with a matched group of patients without R.T.A. In this series the most obvious difference between the 2 groups was the very high incidence of chronic pyelonephritis in those with R.T.A. These authors considered this to be an aetiological factor. However, evidence of acute or chronic infection was only present in 30% of our patients with R.T.A. Barcelo and Pinto (1972) reported an 18·6% incidence of R.T.A. in a series of 300 recurrent stone formers and commented on the absence of urinary infection in this group.

Irrespective of treatment, the overall incidence of recurrence or significant change in stones left *in situ* was 30% in those with normal metabolic studies. This compares with 70% in those patients with idiopathic hypercalciuria, 77% in those with R.T.A., 64% in those with both idiopathic hypercalciuria and R.T.A. and 42% in those with infection alone. With such a high incidence of recurrence or significant stone change in patients with abnormal metabolic studies, when compared to those with no detected abnormality, we feel that long-term follow-up is essential.

This contrasts with the views of Powis *et al.* (1974) who were unable to justify long-term follow-up of stone formers. In their survey they attempted, but were unable, to define objective criteria whereby patients likely to suffer recurrent calculi could be identified. They were unable to find any helpful difference in the prevalence of abnormal urine or serum biochemistry. However, in their series there was a very low incidence (22·9%) of biochemical abnormalities when compared to this series where 60% of the patients had a biochemical abnormality.

The reason for the apparent low incidence of metabolic stone disease in Birmingham is hard to define. It is not clear whether they looked for the incomplete form of R.T.A. in their patients. 21% of our patients had this abnormality which formed our second-largest group of disorders. In Powis's series, as in our own, idiopathic hypercalciuria was the commonest metabolic abnormality. In our series 70% of these patients either produced another stone or the stone *in situ* enlarged significantly in size but only 32·5% in Powis's series produced recurrent stones. This may be accounted for by their taking a urine Ca^{++} excretion of 300 mg/24 hours as the upper level of normal, whereas we have taken 350 mg/24 hours. Because of this very high incidence of change we feel that it is reasonable that patients who have had the metabolic investigations shown in Table I and are found to have an abnormality should be followed-up.

It has been possible for a number of years to treat these metabolic disorders. Yendt *et al.* (1970) have reported a highly significant reduction in the recurrence of new calculi or changes in remaining calculi with hydrochlorothiazide therapy. Similarly, Rose and Harrison (1974) report a very strong clinical impression that renal stone formation has not progressed in their patients in whom control of urinary Ca^{++}, using diuretics or cellulose phosphate, was obtained.

Murphy (1972) has reported a similar decrease in renal stone production in patients with incomplete R.T.A. treated with potassium citrate.

However, the therapy required especially to lower urine Ca^{++} output is not without side effects. In Yendt's series (1974), 3 patients out of 68 had to stop treatment because of side effects. 25 other patients had side effects attributable to the use of hydrochlorothiazide. These were weakness (12), increased thirst (9), light-headedness (9), constipation (3), loss of libido (3), increased urination (2), arthralgia (2) and rash (1). Hyperuricaemia occurs commonly in patients on thiazide therapy and this is occaionally seen with overt attacks of gout. Thiazides are also known to induce diabetes mellitus and this possibility must be considered. Hypokalaemia may require correction in certain patients but this correction may result in increased urine Ca^{++} excretion.

The long-term effects of magnesium deficiency, a known complication of diuretics, are not yet fully assessed, although metastatic calcification seen in animals has not been reported in humans.

Cellulose phosphate has also been used to lower urine Ca^{++} excretion with good result, although in the series reported by Rose and Harrison (1974), 25% of patients had to stop treatment because of side effects. Recent studies by Pak, Delea and Bartter (1974) suggest that idiopathic hypercalciuria may constitute at least 2 separate entities, "Renal hypercalciuria" and "absorptive hypercalciuria", the former responding to diuretics and the latter to cellulose phosphate. Until there is a clear-cut understanding of the pathogenesis of the hypercalciuria, approaches to medial treatment will be hampered.

Although 70% of our patients with idiopathic hypercalciuria had some change in their stone studies during their follow-up, compared with only 30% of those patients with normal metabolic investigations this still leaves 30% with idiopathic hypercalciuria in whom no change occurred. Recently, Marshall *et al.* (1975) reported a gradual fall off in stone recurrence rate in men with idiopathic hypercalciuria over the course of 10 years.

In the light of these findings and the reported side effects of treatment we feel that a controlled clinical trial of treatment against no treatment is required in patients with stones associated with metabolic disorders.

Summary

In a series of 120 patients with renal stones 60% were found to have a treatable metabolic abnormality. Idiopathic hypercalciuria and the incomplete form of renal tubular acidosis were the two most common abnormalities. Both conditions in the untreated form were associated with an unacceptably high stone recurrence rate and incidence of change. In view of this, follow-up is considered essential and if medical treatment is to be offered this should be in the form of a controlled clinical trial.

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The Technique and Results of Pyelocalycotomy for Staghorn Calculi

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It is now generally accepted that the treatment of staghorn renal calculi in patients who are otherwise fit is surgical removal. It is primarily undertaken to prevent further renal damage and extension of stone formation as a result of urine infection and obstruction. The long-term complications of renal failure, pyonephrosis and perinephric abscess are thus usually prevented and the patient is relieved of pain.

The prevention of recurrent stone formation depends upon the complete clearance of the stone fragments and upon the sterility of the urinary drainage system thereafter.

Three principal surgical techniques of stone removal have emerged:

1. Pyelolithotomy; this has been developed by Gil-Vernet (1964) to the logical extent of the sinus approach.
2. Pyelo-nephro-lithotomy; inferior pyelocalycotomy providing the most rational and versatile version of this procedure (Turner Warwick, 1965).
3. Nephrotomy has evolved with the use of local hypothermia (Cockett, 1961; Graves, 1963; Hanley, Joekes and Wickham, 1968); Boyce (1969) has further developed the anatrophic intervascular incision providing good calyceal exposure and the facility of creating a unilocular pelvi-calyceal system by intra-renal calyco-calycostomy.

Each of these techniques has advantages and disadvantages; none is ideal for all cases. The indications for each technique overlap considerably so that the selection of procedure most commonly depends upon the personal preference of the surgeon.

Inferior Pyelocalycotomy

Inferior pyelocalycotomy represents the middle-of-the-road approach between pyelotomy and nephrotomy; it can be used for the great majority of cast calculi and the purpose of this paper is to discuss our experience and our results with it over a 10-year period. Its particular advantages are:

1. Lower pole nephrotomy provides an open exposure of the pelvis and good access to the middle and lower calyces which can be explored by direct vision calycoscopy.
2. The minimal incision in the lower pole of the kidney provides maximal intrarenal exposure of the pelvi-calyceal system and avoids sizeable vessels.
3. Arterial occlusion and cooling are seldom necessary.
4. Inferior calycotomy provides three options of closure technique.
    - (*a*) Simple closure (Fig. 1*b*).
    - (*b*) Side-to-side uretero-calycostomy to improve the ureteric drainage of the pelvi-calyceal system (Fig. 2).
    - (*c*) Retrograde partial nephrectomy for the accurate removal of a disproportionately damaged calyco-parenchymal segment (Fig. 3).

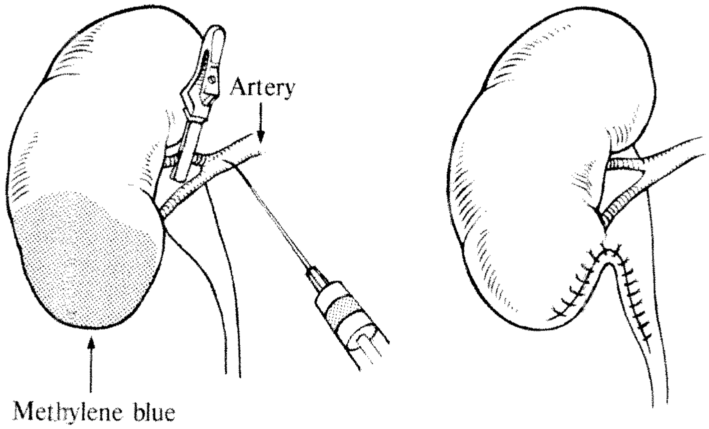

Fig. 1. (*a*) Intersegmental incision located by selective intra-arterial dye injection. (*b*) Inferior pyelocalycotomy and simple closure.

Points of Operative Technique

Supracostal Incision: We generally prefer an 11th or 12th supracostal incision, depending on the length of the 12th rib (Turner Warwick, 1965). Not only is this incision easier to open and close than a rib resection procedure but the fully mobilised rib itself retracts the posterior angle of the incision to provide an exposure which is distinctly superior to that provided by the equivalent rib resection and also lumbotomy (Gil-Vernet, 1964; Harbison, 1974), although this has some compensatory advantages.

Per-operative Renal Radiography: Per-operative renal radiography is essential to ensure complete stone removal in the great majority of cast calculi and an isolated renal radiograph seems to provide the most accurate technique; it is particularly helpful to take both plain and pelvi-injection pyelogram films before opening the pelvis (Turner Warwick, 1965).

Inferior Pyelocalycotomy: Full mobilisation of both the kidney and the renal pedicle is important for effective lower pole pyelocalycotomy so that the kidney can be retained with the lower pole tilted up. The inferior border of the renal pelvis is incised between stay sutures; a malleable probe passed into the lower calyx to emerge through the lower polar tissue facilitates accurate calycotomy. Haemostasis of the margins of the parenchymal incision is achieved by a few temporary full-thickness calyco-capsular stay sutures which provide convenient retraction. Renal pedicle occlusion is not necessary though it may provide a momentary convenience.

No sizeable vessels are divided by lower pole calycotomy and even a random median incision rarely devascularises more than a few millimetres on one side or the other.

Intersegmental Calycotomy: The site of an accurate intersegmental incision between vascular territories can be determined by a selective intra-arterial dye injection when necessary. The injection is most conveniently made into the main renal vessel distal to an occluding clamp with the collateral branches also being temporarily occluded for the duration of the injection (Fig. 1*a*); the margin of the dye-stained area is naturally relatively avascular (Boyce, 1969). This technique is used when the possibility of a simple closure of inferior calycotomy is envisaged since it is important not to leave even a narrow margin of devascularised parenchyma; it is less important

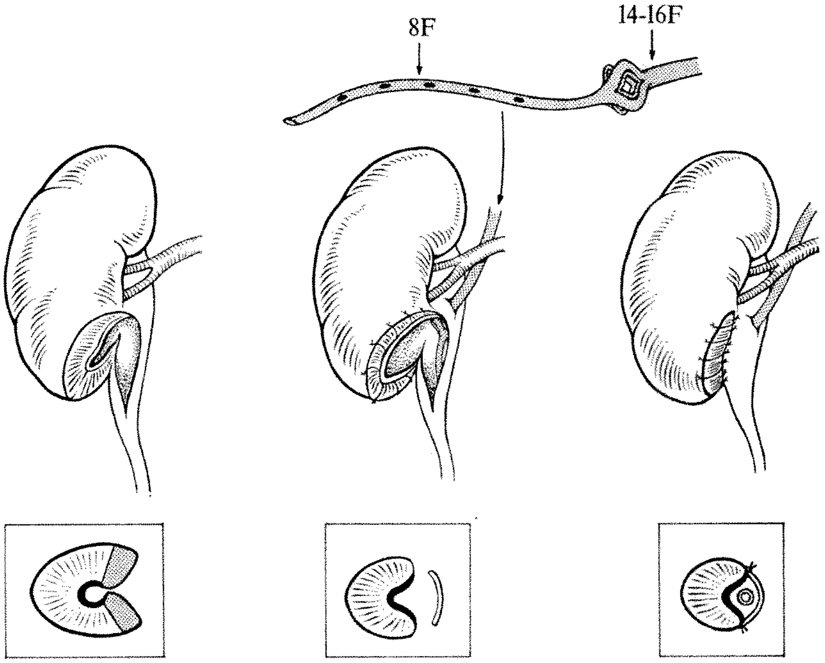

Fig. 2. Inferior pyelocalycotomy and uretero-calycostomy.

for a uretero-calycostomy or a partial nephrectomy since, for these, both margins of the parenchymal incision require further resection.

Stone Extraction: It is remarkably easy to remove even large branched calculi through an inferior pyelocalycotomy; the calyceal extensions can usually be extracted from the calyces unless they are particularly waisted in which case the necks of the calculi are divided for subsequent piecemeal removal.

Instrumentation for Calyceal Exploration: Inferior pyelocalycotomy opens the lower calyx entirely and exposes all but the upper pole calyces for direct internal calycoscopy; this is greatly facilitated by a fibre-light sucker of appropriate design and lightweight intracalyceal stone forceps; the neck of the calyx being triangulated by the open blades for direct inspection (Fig. 4). A lightweight malleable spoon and a fibre-light calyceal neck retractor may also be useful.

External Calycotomy: External calycotomy is quite frequently required for the removal of stones in the upper calyx unless the neck is sufficiently wide although a pyeloscope or a simple cystotelescope has sometimes been helpful. External calycotomy is sometimes required to remove dumb-bell calculi in other calyces; such incisions can often be sited on the margins of a dye-segment injection and a short period of pedicle occlusion may be helpful particularly if the parenchyma is thick.

Uretero-Calycostomy: This is performed by side-to-side anastomosis of the inferior uretero-pyelo-calycotomy. This has been the most commonly employed method of closure in this series.

Some special points of technique contribute to the safety of this procedure. It is of prime importance that the renal parenchyma should not be allowed to surround the ureteric anastomosis and thus create obstructive encircling healing fibrosis. In general, a uretero-calycostomy is

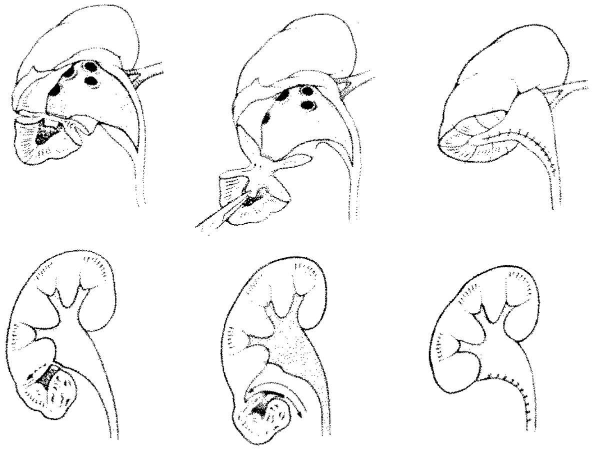

Fig. 3. Inferior pyelocalycotomy and retrograde partial nephrectomy.

facilitated by a dilated calyceal system; meticulous attention to detail is necessary to keep out of trouble when using the technique for an undilated calyceal system. The tip of the lower pole must be resected so that the inferior calyx is spread out by calyx-to-capsule sutures to provide a flattened surface to which the spatulated upper ureter can be applied and sutured (Fig. 2); we routinely used effective stenting pyelostomy drainage to cover this procedure.

Retrograde Partial Nephrectomy: Partial nephrectomy for lower pole calculi is not often indicated. It is only used when the lower calyx or its overlying parenchyma is disproportionately damaged and this can often only be precisely assessed after pyelocalycotomy. It should never be used merely to remove the so-called "sump" of the lowermost calyx for another will take its place. A uretero-calycostomy is more appropriate.

Selective removal of one or more calyces together with exactly that part of the parenchyma which drains into it can only be accurately achieved by retrograde partial nephrectomy (Fig. 3) (Turner-Warwick, 1965). The neck of the calyceal system selected for resection is divided and peeled outwards so that a plane of cleavage is developed through the cortex outside the appropriate renal pyramid. Vessels traversing this urinary drainage territory are suture ligated. It is often impossible to achieve a satisfactory reapproximation of the parenchyma to overclose the pelvic suture line after an anatomically accurate retrograde partial nephrectomy; we commonly support this by omental pedicle graft. The standard surgically convenient blind-wedge technique of parenchymal resection bears no relation either to parenchymal drainage of vascular territory and belongs to a bygone age of renal surgery.

Pyelostomy and Stenting: We routinely use the Cummings combined form of pyelostomy and stenting for uretero-calycostomy and any other precarious upper tract anastomosis, to avoid the risk of urinary extravasation we prefer this to separate stenting and drainage. Whatever form of ureteric stenting is used we think it important that this should be fenestrated to facilitate the re-entry of exudates and of urine that has been propelled into the space round the catheter by peristalsis. We also prefer to insert this as a pyelostomy and so avoid parenchymal damage unless an external calycotomy has already created a suitable nephrotomy. In using a Cumming's catheter it is important to cut a small wedge out of the distal cone so that end-on compression of the winged zone does not occlude the drainage aperture.

The Omental Wrap: Peri-renal tissue is poorly developed to resist infection and this commonly results in dense fibrosis. The omentum not only greatly helps healing but retains its suppleness to

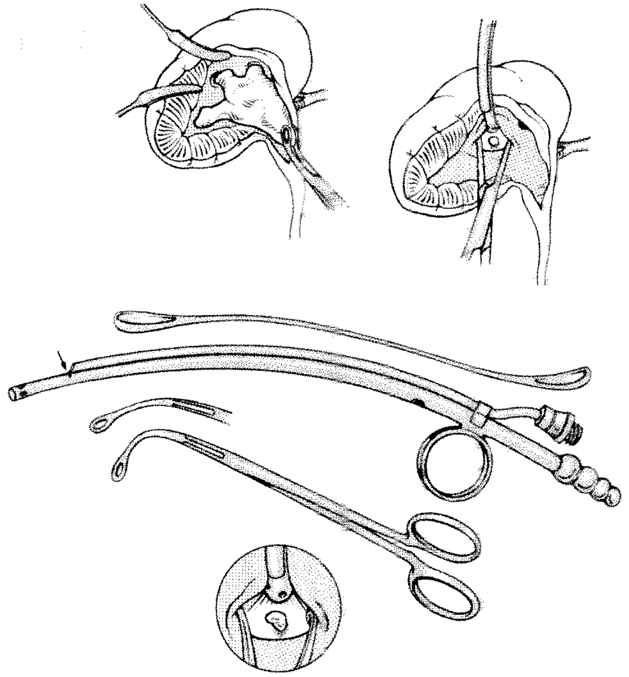

Fig. 4. Inferior pyelocalycotomy, removal of main calculus and calycoscopy.

allow urodynamic mobility; it also facilitates any subsequent re-exploration that may be necessary (Turner Warwick, 1967, 1975). We routinely use an omental wrap to support complex repairs of both the upper and lower urinary tracts.

It is usually relatively easy to mobilise sufficient omentum to reach the kidney and upper ureter through a peritoneal incision in front of the ascending or descending colon, although this may occasionally be compromised by abdominal adhesions. The blood vessels supplying the omentum descend vertically from the gastro-epiploic arch so that the apron can be divided between adjacent vessels and mobilised from the transverse colon.

Postoperative Pyelostomy Drainage: A pyelostogram is routinely performed about the 12th post-operative day to verify healing of the suture-line and to exclude extravasation before it is removed.

Stone Solvent Irrigation

Even with meticulous technique it is sometimes inevitable that minute fragments of calculi are left behind after pelvi-calyceal exploration, whatever technique is used.

Postoperative irrigation with stone solvents such as Renacidin must be undertaken with great care since they are naturally tissue irritants (Cunningham, Friedland and Stamey, 1973). We have frequently used Renacidin in this series, especially when the calculus was particularly friable. The irrigation is not started until the postoperative pyelostogram has proven healing without extravasation and we have had no adverse reactions.

Radiographic evaluation of the irrigating efficiency has suggested that with the Cummings combination of combined pyelostomy and urethral stenting, an intermittent irrigation is more efficient to avoid "streamlining" down the ureter. The reservoir is set at low level, about 30 cm above the kidney, the intermittent irrigation can often be conveniently operated by the patient during the day, the clamp on the tube being released every half-hour during the day and replaced when an appropriate volume, say 20 ml, has been run in.

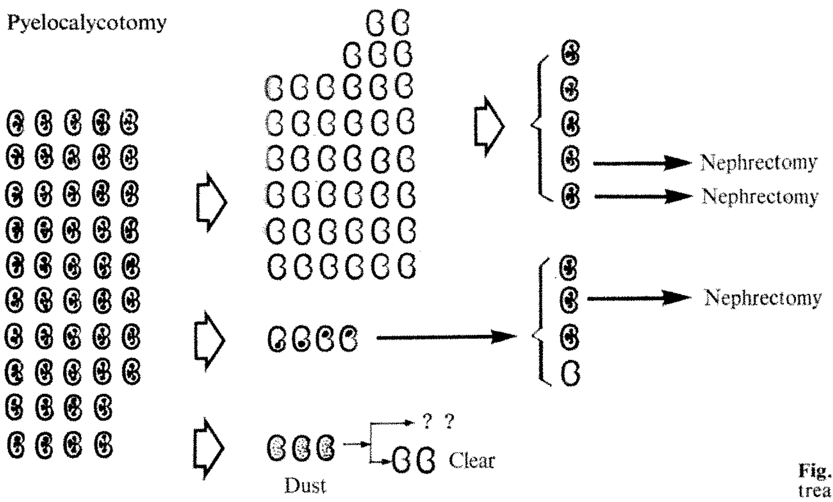

Fig. 5. Fate of 48 kidney stones treated by Pyelocalycotomy.

The Present Series

58 calculi were included in the series of which 42 fulfilled the criteria for a staghorn—the whole of the pelvis and at least 2 major calyces being occupied by stone. There were 14 multiple calculi and 2 in which only 1 major calyx was involved. For the sake of comparison the results include 10 patients who were treated by a Gil-Vernet approach.

Age Incidence: There was a uniform spread from the 3rd to the 8th decade, the youngest being 20 and the oldest 76.

Sex Incidence: There were 25 males and 28 females—unlike most series which have a male predominance.

Side: There were 27 on the right and 31 on the left, thus 5 were bilateral.

Follow-up: Patients have been followed up for periods varying from under a year to 10 years.

Causes of Stones: The majority of stones were infective in origin but there were a small number of other aetiology:

Infective	38
Hypercalciuria	4
Hyperparathyroidism	4
Neuropathic bladder	3
Pelvi-ureteric obstruction	2
Recumbency	1
Medullary sponge kidney	1
Cystinuria	1

Preoperative Infection

35% had *Proteus*, 28% had coliform and 30% were sterile at the time of preoperative assessment.

Results

Gil-Vernet

Of the 10 patients only 5 remained stone-free and sterile. 2 patients had retained stones which enlarged in the presence of continued infection. 2 further patients remained infected (with *Proteus*) and both developed further calculi, 1 in a poorly functioning kidney which came to nephrectomy and the other in a patient who proved to have a parathyroid adenoma. 1 patient died of haemorrhage on the 2nd postoperative day.

Thus in this group, radiological clearance of all calculi was achieved in 8 cases (80%) and 4 patients (40%) remained infected, all of whom developed recurrent calculi or extension of their residual stone.

Pyelocalycotomy (Fig. 5)

48 kidneys in 44 patients fell into this group. Of these 41 were radiologically cleared of stone leaving residual calculus in 7 (15%). Of those that were cleared 10 (25%) remained infected at follow-up and 5 of these developed further calculi. However 1 of these was in a paraplegic and 2 in very poorly functioning kidneys at the time of surgery which eventually came to nephrectomy.

Of those 7 who had retained stone, 3 had "dust" present, 3 had fragments left and in 1, some spongy matrix was missed at surgery which was washed out with Renacidin in the immediate postoperative period. Renacidin was also effective in clearing one of those in whom dust was left behind and in another the particles passed spontaneously. The other patient with "dust" was lost to follow-up.

In the 3 patients in whom actual fragments were left, 1 remained unchanged, 1 required further clearance (in a medullary sponge kidney) and 1 came to nephrectomy in a poorly functioning organ. Thus the overall recurrence rate was 17% (8 kidneys), although for those kidneys in which the aetiological course was purely infective and had measurable function at surgery recurrence rate was 6%. Furthermore, in all but 3 patients (in both groups) who developed further calculi or in whom residual calculi enlarged the infecting organism was *Proteus*. Only 1 was infected with *E. coli* and both the others had persistent *Pseudomonas* (1 of whom had an ileal loop).

Renacidin: Renacidin was used on 8 occasions and in 2 kidneys residual specks or matrix were cleared.

Transfusion Requirements: Blood transfusion was not required in 47% of cases; 30% received 1 unit and 18% 2 units. In only 2 cases was more required—4 units in 1 and 6 in the other in whom secondary haemorrhage occurred.

Discussion

In our experience pyelocalycotomy has proved a more reliable procedure. All patients in whom the kidneys were cleared radiologically and were kept sterile remained stone-free. We would agree with Wickham and Mathur (1971) that the likely cause of recurrence is infection with entero-bacteria (almost always *Proteus* in our series) a high urinary pH and a particle of calculus. Furthermore very poor function at the time of surgery predisposes towards recurrent inrection and further stone formation—though nephrectomy was never undertaken as the primary procedure. Singh, Marshall and Blandy (1975) have shown that particles less than 2 mm in diameter may not show on pre-operative X-rays and it seems possible that some of those patients who were radiologically cleared and had recurrence subsequently may have had minute particles left as an infected nidus. Equally, it seems likely that had better bacteriological control been effected in those which remained infected but were cleared of calculi some recurrent stones might have been avoided, especially in kidneys with poor function.

Furthermore, metabolic and anatomical anomalies were responsible for the regrowth in some instances.

Inferior pyelocalycotomy greatly facilitated the removal of calculi, and subsequent uretero-calycotomy improved drainage without sacrificing function parenchyma.

The stone instruments are supplied by Thackrays and by Down Brothers and the fibre light sucker by the Genito Urinary Manufacturing Co., London.

Summary

In 10 kidneys treated by the sinus approach the overall recurrence rate was 40%.

In 48 kidneys treated by pyelocalycotomy the overall recurrence rate was 17% but only 6% in functioning kidneys with infective stones.

Infection was controlled in 75% of patients from whom all stone fragments were removed radiologically but all patients in whom fragments remained, or who developed further calculi, remained infected—with *Proteus* in 75% of cases.

All patients with kidneys completely cleared of calculi in whom infection was controlled remained stone-free for periods of up to 10 years.

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The Place of Partial Nephrectomy in the Management of Renal Calyceal Calculi

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Many calyceal stones give rise to no symptoms and remain unchanged in radiographs year after year. Others soon work loose and find their way into the ureter, where they occasionally get held up and require the use of Dormia's basket or the safe and easy operation of ureterolithotomy. Hamilton Stewart noted that some of these calyceal calculi recurred again and again in the same place and this led to his enunciation of the stone-nest theory and to its logical consequence, the operation of partial nephrectomy (Stewart, 1952, 1955), whereby it was hoped that further stone formation would be prevented. Stewart's excellent results were confirmed by some but not by others (Williams, 1963; Papathanassiadis and Swinney, 1966; Myrvold and Fritjofsson, 1971). Uncertainty as to when it was necessary to remove the stone, when it was safe to leave it alone and above all, as to when it was advisable to remove the parenchyma by partial nephrectomy, made many surgeons question the role of partial nephrectomy, especially since the development of Gil-Vernet's sinus approach to the calyx made it possible to extract stones without cutting into the parenchyma at all. It was in the hope of resolving some of these uncertainties that we set out to examine our own results. We hoped to find out whether it was true, for example that calyceal stones were really more prevalent in the lower than in the other calyces of the kidney; whether they tended to recur in the same, or in other calyces; what was the relationship between hypercalciuria and these calyceal calculi; whether urinary infection was improved by removing them; what happened to those patients in whom these little stones were left alone and just followed up; and whether there were fewer recurrences in those treated by partial nephrectomy than by pyelolithotomy or nephrolithotomy.

The Series

The present study has been carried out on 416 patients attending a Stone Clinic from 1967 to 1971 inclusive. Not all patients with stones attending the London Hospital during this time were referred to the Stone Clinic and in particular the series excludes those with large staghorn calculi, who have formed the subject of other studies (Singh *et al.*, 1971; Blandy and Singh, 1975) since we believe that the problems of the staghorn stone are quite different. Some cases with hyperparathyroidism and other metabolic conditions who were attending other clinics in the hospital were not included in this series which formed the basis of a previous communication (Marshall *et al.*, 1975).

There were 173 women and 243 men in this series. By *recurrence*, we mean the appearance of a new stone in serial radiographs. By *infection* we mean 2 consecutive urine cultures showing more than 10^5 bacterial colonies per ml urine after the first stone had been found and after any first infection had been treated with appropriate antibiotics, *i.e.* we were concerned with persistent, not transient infection.

Patients fell into 3 groups: (1) those in whom *no operation* was performed during the period of this study; these patients were seen at regular intervals, no less often than once a year, when a plain radiograph of the kidneys was obtained: (2) those in whom *pyelo- or nephrolithotomy* was performed, using standard techniques (Blandy, 1971) and (3) those in whom *partial nephrectomy* was performed using a modified Semb technique (Blandy, 1971).

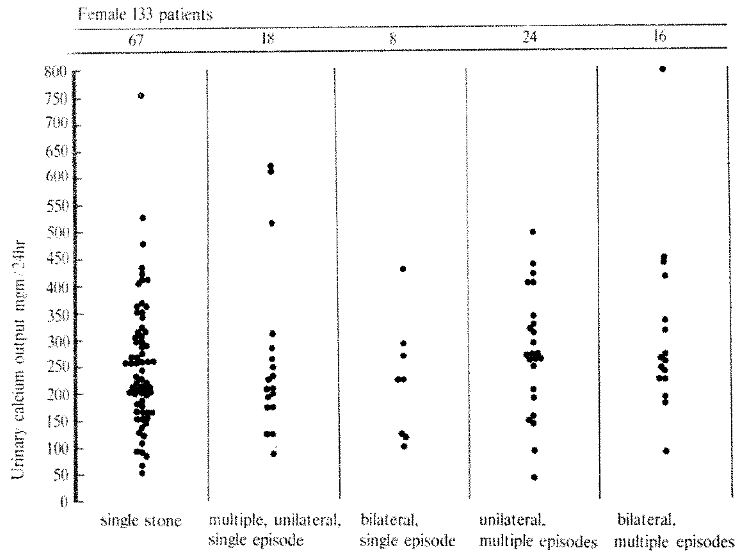

Fig. Urinary calcium excretion in "idiopathic" stone formers.

Results

Site of Stones

80 of 173 females (46%) had single stones, 93 (54%) were multiple, of which 32 were bilateral. 102 of 243 men (45·3%) had single stones; 142 were multiple (54·7%) and were bilateral in 52. The frequency with which these stones were found in the various calyces is shown in Tables I and II: many stones were of course only detected when they had got into the pelvis or the ureter and their site of origin could not be identified but when the stones were first seen in calyces, many more were found in the lower pole than in the other parts of the kidney.

Site of Recurrence

Recurrent stones were found to involve the same calyx in 96% of the recurrences documented in males and 79% of those in females.

Table I

Distribution of Stones
Female: 173 patients

Involvement by stones
(No. of times)

	R	L
Upper calyces	10	9
Middle calyces	8	3
Lower calyces	31	46
Pelvis	14	17
Ureter	27	26

Table II

Distribution of Stones
Male: 243 patients

Involvement by stones
(No. of times)

	R	L
Upper calyces	13	10
Middle calyces	13	17
Lower calyces	47	93
Pelvis	17	30
Ureter	68	74

Table III

Distribution of Lower Pole Stones

	Male	Female
Confined to one lower pole	41	34
In both lower poles	8	5
Associated with stones in other parts of contralateral kidney	6	8
	55	47
No. of lower poles containing stones	63	52

Table IV

Recurrence of Lower Pole Stones

	No. of lower poles	No. of recurrences	Av. length of F.U.
No operation			
Male	49	12	6·3
Female	32	2	6·7
	81	14	6·5
Pyelo/nephrolithotomy			
Male	9	5	13·0
Female	14*	8	5·1
	23	13	8·1
Partial Nephrectomy			
Male	5	0	9·4
Female	8*	0	9·4
	13	0	9·4

* Two patients who had pyelolithotomy subsequently had partial nephrectomy.

Recurrence and Urinary Calcium Output (Fig.)

In those patients in whom the 24 hour urinary calcium output had been measured after the first stone had been discovered and before any recurrence had been noted, it was compared with the pattern of the site and recurrence of stones. As in our previous study (Marshall *et al.*, 1975) the range of calcium output was very similar in both men and women, irrespective of whether their stones were single, multiple, unilateral or bilateral.

Fate of Lower Pole Calculi

Lower pole stones were present in 47 of the 173 women, 55 of the 243 men and were bilateral in 5 women and 8 men, so that there were altogether 115 lower poles containing stones available for

Table V

Number of Lower Pole Stones vs. Recurrence Rates

	No. of lower poles	No. of recurrences	Recurrence rate (%)	Av. length of F.U.
No operation				
Single stone	41	1	2·4	6·3
Multiple stones	40	13	32·2	6·7
Pyelo/nephrolithotomy				
Single stone	9	1	11·0	8·3
Multiple stones	14	12	85·7	8·0
Partial nephrectomy				
Single stone	6	0	0	10·0
Multiple stones	7	0	0	8·7

study (Table III). We examined their records to determine how recurrence of stones was related to their management and to whether the stones were at first single or multiple.

(a) Group treated by Observation—no Operation

There were 81 lower poles with stones which were not operated on during the period of this study (Table IV). In 71 instances the stone either remained unchanged, or passed spontaneously down the ureter. In 10 cases a ureterolithotomy was required. During the period of the follow-up new stones formed in 14 of these kidneys (17%) but almost all these recurrent stones were seen in lower poles which had originally contained more than one calculus. There was only 1 recurrence in 41 lower poles with a single stone to start with and 13 in the 40 lower poles with multiple stones at first (Table V).

(b) Lower Poles treated by Pyelo- or Nephrolithotomy

Stones were removed by pyelo- or nephrolithotomy from 23 lower poles. Recurrence took place in 1 of the 9 in whom the stone was originally single but in 12 of the 14 where the stones were at first multiple.

(c) Lower Poles Partial Nephrectomy

There was no recurrent stone formation in any of the 6 kidneys with single stones in the lower pole, or the 7 kidneys with multiple stones, after partial nephrectomy.

Relationship of Calyceal Stones and Infection

Only 5 of the men (9%) had persistent infection so that it was not possible to evaluate its role in male patients. In women the infection rate was much higher—47%—but it did not seem to be influenced by the way the stones were treated (Table VI).

Discussion

In this series we found that the lower calyces were the most common site of origin for these small stones and that recurrence usually affected the same part of the kidney as the original stone. So far the results support Hamilton Stewart's concept of the "stone nest". Judged by the number of recurrences which took place in the various groups of patients, we could find no relationship

Table VI

Infection in Female Patients with Lower Pole Stones

(*After first stone episode ± operation*)

	No. of lower poles	Infected	%
No operation			
Single stone	18	7	39
Multiple stones	14	5	36
	32	12	37·5
Pyelo/nephrolithotomy			
Single stone	6	1	16·6
Multiple stones	8	7	87·5
	14	8	57·0
Partial Nephrectomy			
Single stone	4	2	50
Multiple stones	4	1	25
	8	3	37·5

In the 5 patients with bilateral stones, each pole was given the same designation.

between the numbers of stones or their frequency of formation and the urinary calcium output; this want of correlation with so-called hypercalciuria was noted in our previous study. It was also disappointing to find no clear relationship between the presence of infection and the recurrence rate of these small stones, though in the case of the large staghorn calculi, it was obvious that infection played a major role in their persistence and recurrence (Singh *et al.*, 1971; Blandy *et al.*, 1975).

As to the question of the indication for partial nephrectomy, our studies afford some practical guidelines. In the first place, when the stones are single and occupying the lower pole, it would seem reasonably safe to leave them alone when they are not giving rise to symptoms. In 41 such cases only 1 had a recurrence and the chance of a patient subsequently needing a ureterolithotomy in the entire group was only 1:8.

When it was thought necessary to remove a single polar stone there was no significant difference in the recurrence rate after removal by pyelo- or nephrolithotomy and lower pole partial nephrectomy, which in these small numbers does not differ significantly either from the results obtained by Stewart (1955) or Williams (1963).

Where the stones in the lower pole were originally multiple, then the situation was quite different and here the zero rate of recurrence after partial nephrectomy was clearly much better than the recurrence rate of 32·2% in those patients who were merely observed and of 85·7% in those treated by nephro- or pyelolithotomy ($P < 0·05$).

These findings suggest that partial nephrectomy should be reserved for those cases in which the calyceal stones are multiple and causing symptoms but that sacrifice of renal parenchyma is not justified when polar calculi are single to start with. This may be helpful in deciding what is best for the patient whose polar calculi are present on both sides, which in our series was the situation in 10% to 15% of cases.

Obviously the decision to operate on these kidneys will often be influenced by the amount of destruction and scarring which has taken place in the affected pole of the kidney and where the lower pole is frankly useless it would seem sensible to remove it. But our previous hopes that removal of the stone and its surrounding parenchyma would help in controlling persistent infection have been disappointed.

Summary

In 416 patients with renal and ureteric calculi other than large staghorns we found that when it was possible to identify the calyx of origin of the stones, the lower poles were involved in 36·6% of males and 40·4% of females.

In the follow up of the 115 lower poles originally containing stones the recurrence rate was 17% in those who were merely observed, 56% in those treated by pyelo- or nephrolithotomy, and zero in those treated by partial nephrectomy. But when these cases were looked at more closely it was found that recurrences were virtually confined to lower poles which had originally harboured more than one stone, while in those with single stones to start with, the recurrence rate was not significantly different in either of these three groups.

Partial nephrectomy should therefore be reserved for selected cases where the stones are originally multiple, or where the lower pole has been severely damaged. It is not necessary for small and single calyceal calculi.

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Urinary Gamma-glutamyl Transpeptidase, an Indicator of Renal Ischaemic Injury and Homograft Rejection

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The cells of the kidney most sensitive to ischaemic injury are those of the proximal convoluted tubules (Koletsky and Gustafson, 1947; Oliver, MacDowell and Tracy, 1951). It is their high energy requirement chiefly for the transport of ions, particularly sodium, that makes them so vulnerable. The first detectable change in the architecture of these cells following ischaemia is the loss of their brush border (Kiser *et al.*, 1961; Reimer, Ganote and Jennings, 1972). A search was therefore made for an enzyme whose location within the kidney was at this site and such an enzyme is gamma-glutamyl transpeptidase (γ-GT).

The activity of γ-GT can be detected in mammalian tissues and is highest in the kidney. If the relative activity of γ-GT in the kidney is taken as 100, then the relative activity of other tissues as measured by Orlowski and Meister (1970) are shown in the Table.

Table

Tissue Activity of γ-GT

Organ	Relative activity
Kidney	100·00
Pancreas	8·30
Liver	3·90
Spleen	1·50
Brain	0·50
Lung	0·31
Skeletal muscle	0·067
Cardiac muscle	0·045

Histochemical studies have localised it to the brush border of the proximal convoluted tubule and some parts of the loop of Henle but not in the glomeruli or collecting ducts (Albert, Orlowski and Szewczuk, 1961; Glenner, Folk and McMillan, 1962). The enzyme catalyses the hydrolysis of the γ-glutamyl bond of reduced glutathione and mediates the transfer of amino-acids or peptides for the cysteinyl glycine of reduced glutathione, to form the corresponding γ-glutamyl peptide (transpeptidation) in the γ-glutamyl cycle. The enzyme is very stable between +20°C and −20°C and samples can be stored for many months without loss of activity. Its presence has been demonstrated in canine and in human serum and urine (Orlowski and Szewczuk, 1962) and its assay is simple.

Objective

The objective of the following experiments was to determine whether plasma and urinary γ-GT activity was increased (*a*) following renal ischaemia in experimental animals, (*b*) following renal ischaemia in man, and (*c*) following renal transplant rejection, one component of which is ischaemia of the graft and in all three to attempt to ascertain whether the degree of γ-GT activity was directly related to the degree of ischaemic injury.

Methods

Experimental Animals

Adult mongrel dogs weighing between 15 and 23 kg, unselected for sex, were anaesthetised with sodium pentobarbital and respired by positive pressure ventilation. The abdomen was opened and the left ureter was cannulated. Cannulae were also inserted into the right femoral artery and vein for monitoring of arterial blood pressure and for venous blood sampling. Normal saline was infused into the right foreleg throughout the experiment and, after a 30-min stabilisation period, blood and urine samples were collected for γ-GT estimation both before and at 15-min intervals for 3 hours following clamping of the left renal artery. The dogs were then sacrificed. 25 dogs were divided into groups of 5 and underwent 5, 30, 60 and 90 min of left renal ischaemia using the standard experimental model described and 1 group underwent mobilisation of the kidney alone, without arterial clamping. 1 other dog underwent 90 min of left renal ischaemia under full sterile precautions and was studied for 8 days.

The assay of γ-GT activity in the plasma and urine was by the kinetic photometric method described by Szasz in 1969.

Results

No significant rise in plasma γ-GT activity could be demonstrated either in the first 3 hours or at any time in 8 days following the ischaemic period.

The urinary γ-GT activity rose dramatically after releasing the arterial clamp following 90 min complete left renal ischaemia from a mean of 112m Units in 15 min to a peak of 8,727m Units in 15 min, a 78-fold increase. There was a 53-fold increase in the only other non-anuric dog. The increased activity fell rapidly but was still 20 times normal after 3 hours.

The results of the groups of dogs undergoing periods of ischaemia varying from 5 to 90 min are expressed as the urinary γ-GT activity in 3 hours (1,000m Units = 1 unit). The urinary γ-GT of a control period was calculated as 0·49 to 1·39 Units in 3 hours. After kidney mobilisation alone there was an increase in urinary γ-GT in all 5 test animals to a mean of 4·43 Units. Following 5 min ischaemia, the mean urinary γ-GT was 13·95 Units, and following 30 min it rose to 38·39 Units. The difference between each group being significant P = 0·004, P = 0·008 and P = 0·048 respectively. After 60 min of ischaemia, however, the mean γ-GT fell and after 90 min, 3 dogs were anuric (Fig. 1).

Urine from the (non-test) contralateral kidney was examined in 2 dogs for increased urinary γ-GT activity following 30 min of ischaemia in the test kidney but all the values were within the control limits.

The normal range of the urinary γ-GT from a single dog kidney was 68·8m Units in 15 min (S.D. 39·72). The upper limit of normal for a 3-hour urinary γ-GT was 2,500m Units.

Discussion

The urinary γ-GT activity being significantly increased following simple mobilisation of 5 min ischaemia suggests that it is a sensitive indicator reflecting cellular injury. Provided that there is adequate urine flow and that the renal insult has not been too severe, then the urinary γ-GT activity could be used as a quantitative measure of tubular cell ischaemia injury. In view of these experimental findings, together with previous studies where the urinary γ-GT was used as a

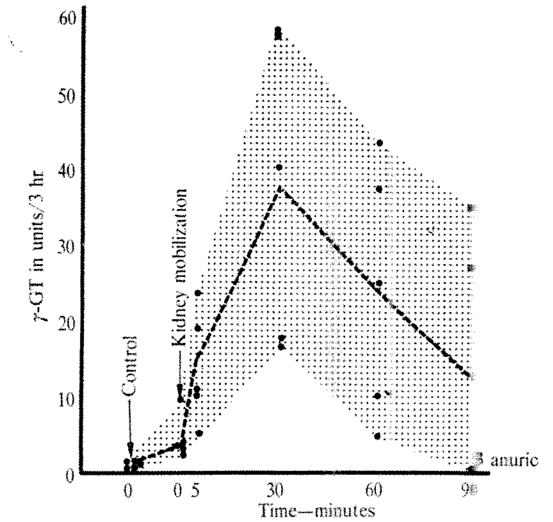

Fig. 1. Canine urinary γ-GT activity following renal ischaemia. Each large dot represents the 3-hour urinary γ-GT of each dog and the dotted line shows the mean.

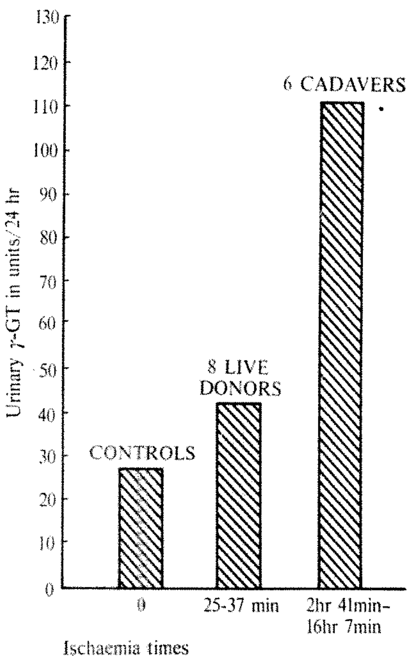

Fig. 2. Urinary γ-GT after human kidney transplantation.

measure of injury in ischaemic canine kidneys protected by hypothermia (Ward, 1975), it would be worthwhile investigating the urinary γ-GT activity in human renal ischaemia.

Human Renal Transplant Studies

The ischaemia time in renal homotransplantation can be measured exactly and provides circumstances whereby ischaemic injury can be measured in man. Similarly those cadaver kidneys maintained for long periods by hypothermic perfusion preservation provide additional sources of study of cellular injury.

1 component of the transplant rejection process is ischaemia of the graft and obliterative lesions occur in the cortical vessels (Porter, Calne and Zukoski, 1964; Dunn and Randall, 1974). It is the ischaemia caused to the tubular cells which forms the basis for γ-GT release studies in the urine of patients experiencing renal transplant rejection episodes.

Methods

Human Studies

20 consecutive patients undergoing renal homotransplantation were studied using either cadaver or living related donors. 24-hour urine collections were made from the day of operation to the day of discharge from hospital and the urinary γ-GT was measured. Transplant donor recipient tissue matching was based on the H-LA and ABO systems as described by Terasaki, *et al.* (1966). Rejection episodes diagnosed using conventional criteria were declared by the attending physician who had no prior knowledge of the γ-GT results. All the patients were treated with routine immunosuppressive agents, azothiaprine, prednisone and anti-lymphocytic globulin and injections of

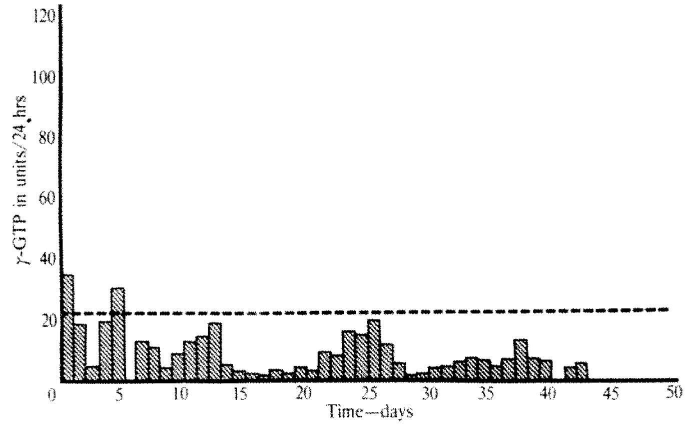

Fig. 3. Urinary γ-GT activity following related donor (A match) renal transplantation (Patient No. 5, J. H.). There was no clinical evidence of rejection.

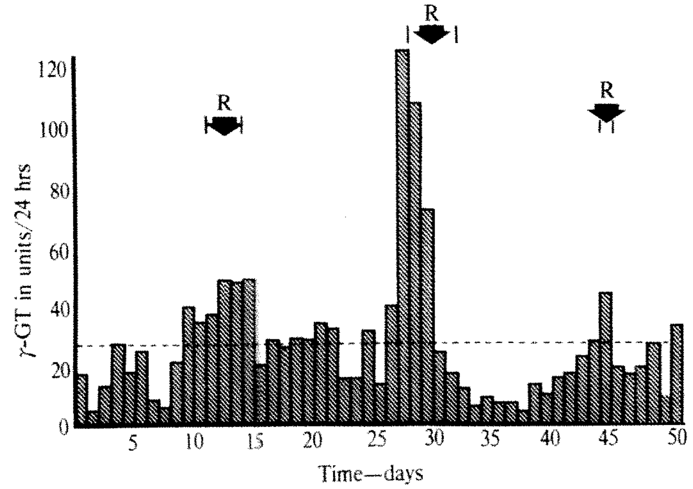

Fig. 4. Urinary γ-GT activity following related donor renal transplantation (Patient No. 13, G. S.). R denotes clinical rejection. A dramatic rise in γ-GT on day 28 was clinically diagnosed as rejection on day 29 and rapidly returned to normal after I.V. prednisolone.

methyl prednisolone sodium succinate during rejection episodes. Prior to transplantation the live donor kidney was flushed with cold perfusate and the cadaver kidneys underwent pulsatile perfusion preservation with cryo-precipitated plasma at 7°C using the Mox perfusion apparatus. 10 healthy adult males were studied as controls, as were 10 adult males with no known nephro-urological disease on prednisone therapy (40 mg daily) for asthma.

Results

The raised urinary γ-GT in the first postoperative 24 hours can be attributed to the specific ischaemic period of the operation and the mode of preservation and raised levels of γ-GT later in the postoperative period possibly to the ischaemia of graft rejection. The control male γ-GT varied from 22·1 to 55·3 Units in 24 hours from 2 kidneys and the control group on prednisone was significantly lower (P = 0·026) from 16 to 40 Units.

Comparing groups of controls, live donors and cadaver donors the results are expressed in Fig. 2. Of the transplanted patients, 8 live donors with ischaemia times of less than 37 min had a mean urinary γ-GT of 42·4 Units in 24 hours. 6 kidneys which underwent perfusion preservation with extracorporeal times varying from 2 hours 41 min to 16 hours 7 min had a mean urinary

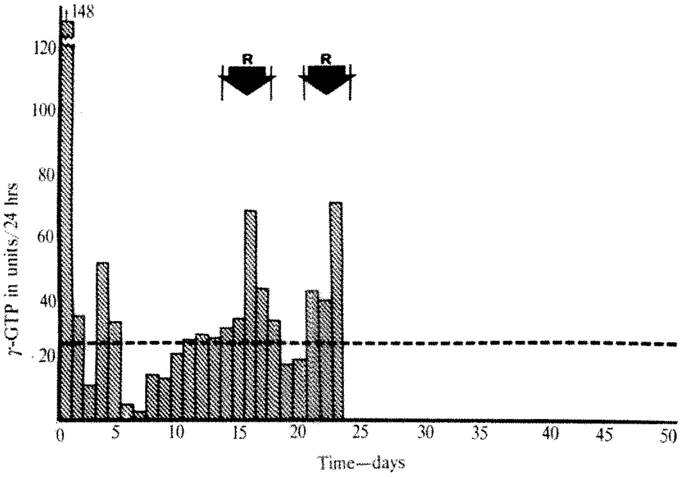

Fig. 5. Urinary γ-GT activity following cadaver donor renal transplantation (Patient No. 7, W. L.). The high γ-GT level on day 1 followed perfusion preservation for 2 hours 41 min. R denotes rejection episodes.

γ-GT of 111·6 Units in 24 hours, explicitly demonstrating increased urinary γ-GT with increasing renal injury.

Considering rejection, 14 such episodes were diagnosed clinically and 12 of these were associated with a raised 24-hour urinary γ-GT activity. On the 48 patient days on which rejection was clinically diagnosed, the mean 24-hour urine γ-GT was 39 Units and the γ-GT on those days with no clinical rejection was less than 27·6. The difference was significant ($P = 0{\cdot}004$).

Detailed examples are presented in the form of histograms, the vertical axis being the 24-hour γ-GT activity and the horizontal axis the time in days post-transplantation (Figs. 3, 4 and 5).

Discussion and Conclusions

At least 15 different urinary enzymes and 16 tissue enzymes have been studied in relation to renal transplant rejection and are included in reviews by Raab (1972) and Ward (1975). It is the specific location and concentration of γ-GT within the kidney, however, which gives its special diagnostic potential. This test could aid the physician in managing his patients and could help him estimate the ischaemic injury in kidneys undergoing arterial clamping, in renal preservation or following the operation of transplantation. It may also help confirm the clinical diagnosis of rejection by measuring its ischaemic components. It could also alert him to the possibility of subclinical rejection.

Frank clinical rejection invariably corresponded with a γ-GT activity in excess of 60 Units per 24 hours and the lowest peak in diagnosed rejection was 45 Units. The frequency, however, with which the urinary γ-GT was above the upper limit of normal but without a clinical diagnosis of rejection, suggests that the ischaemic phenomenon probably associated with transplant rejection, occurs without being reflected by changes in conventional renal function tests. It is only when rejection exceeds a certain intensity that a clinical diagnosis is possible.

The great advantage of the measurement of urinary γ-GT is that it is unobtrusive and far more agreeable to the patient than most other nephrological diagnostic measures requiring only a 24-hour urine collection. The assay is simple, quick and inexpensive and while a test is being sought to identify truly the intensity of "immunological rejection", the diagnostic gap can be partly filled by the clinical use of urinary γ-glutamyl transpeptidase activity.

Summary

Gammaglutamyl transpeptidase is an enzyme primarily located in the brush border of the proximal convoluted tubules of the kidney. Its unique localisation in the renal cells most easily damaged by ischaemia and its ease of assay provides the rationale for its use in the measurement of renal ischaemic injury.

Using a standard experimental animal model, canine urinary γ-GT activity was shown to be increased up to 70-fold following 90 min of unilateral renal ischaemia and was significantly raised following only 5 min ischaemia. The urinary γ-GT was used as a measure of ischaemic injury associated with renal transplantation in man and 20 consecutive patients undergoing kidney transplant were studied by daily 24-hour urinary γ-GT estimations and excellent correlation was obtained between raised enzyme activity and the clinical diagnosis of transplant rejection.

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Equivocal Pelvi-ureteric Obstruction

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From time to time urologists are faced with difficult problems of upper urinary tract obstruction. Neither pyeloplasties nor ureteric re-implants are free from morbidity or even mortality, so it behoves the surgeon to be absolutely sure that the operation is necessary. This may be difficult as in the truly equivocal case radiographic and radio-isotope techniques have severe limitations. However, with the better understanding of urodynamics and the advent of a clinically applicable perfusion (pressure/flow) study (Whitaker, 1973*a* and *c*) it is now not only possible, but practical, to assess accurately the degree of obstruction and hence make a logical decision as to management.

The pelvi-ureteric junction presents a particularly difficult problem because of its tendency to an intermittent obstruction, often with a sudden onset. Although the classical type of idiopathic pelvi-ureteric obstruction usually presents no diagnostic difficulty there are many variations on the theme.

For instance, the findings of a narrowed junction with a little calyceal clubbing and full pelvis makes one suspicious of obstruction (Fig. 1) but are perhaps insufficient evidence by themselves to demand a pyeloplasty. The result is a period of uncertainty for both the patient and the surgeon during which time further X-rays are taken and much time is spent in both the clinic and radiographic departments, often only to find that the subsequent appearances are the same and one remains haunted by the prospect of slow and surreptitious deterioration in renal function. In children this prospect is even more daunting.

The pressure/flow findings and their clinical usefulness in the typical and atypical pelvi-ureteric anomalies will be presented.

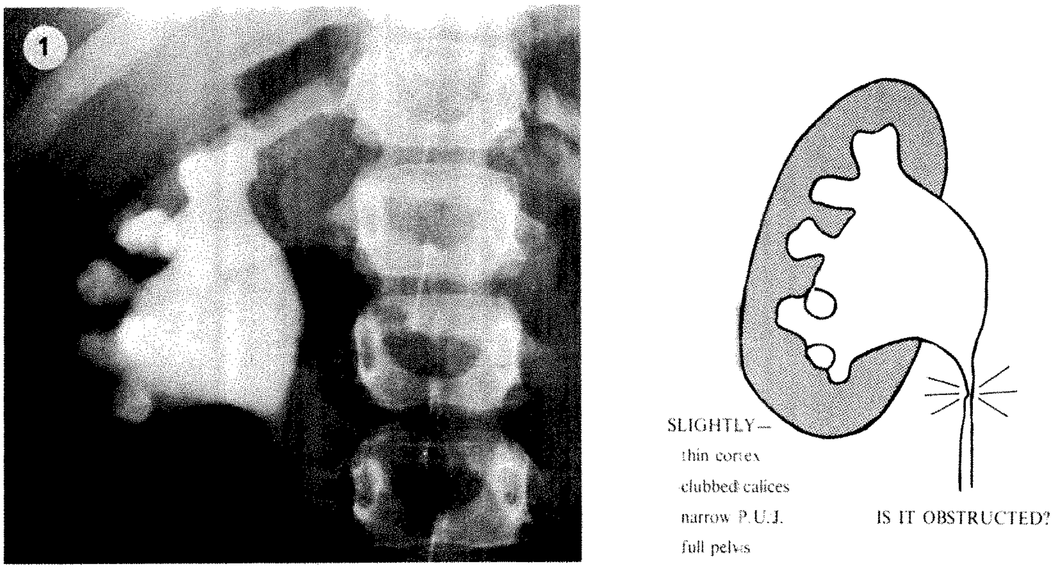


Fig. 1. 11-year-old boy with equivocal obstruction at the right pelvi-ureteric junction.

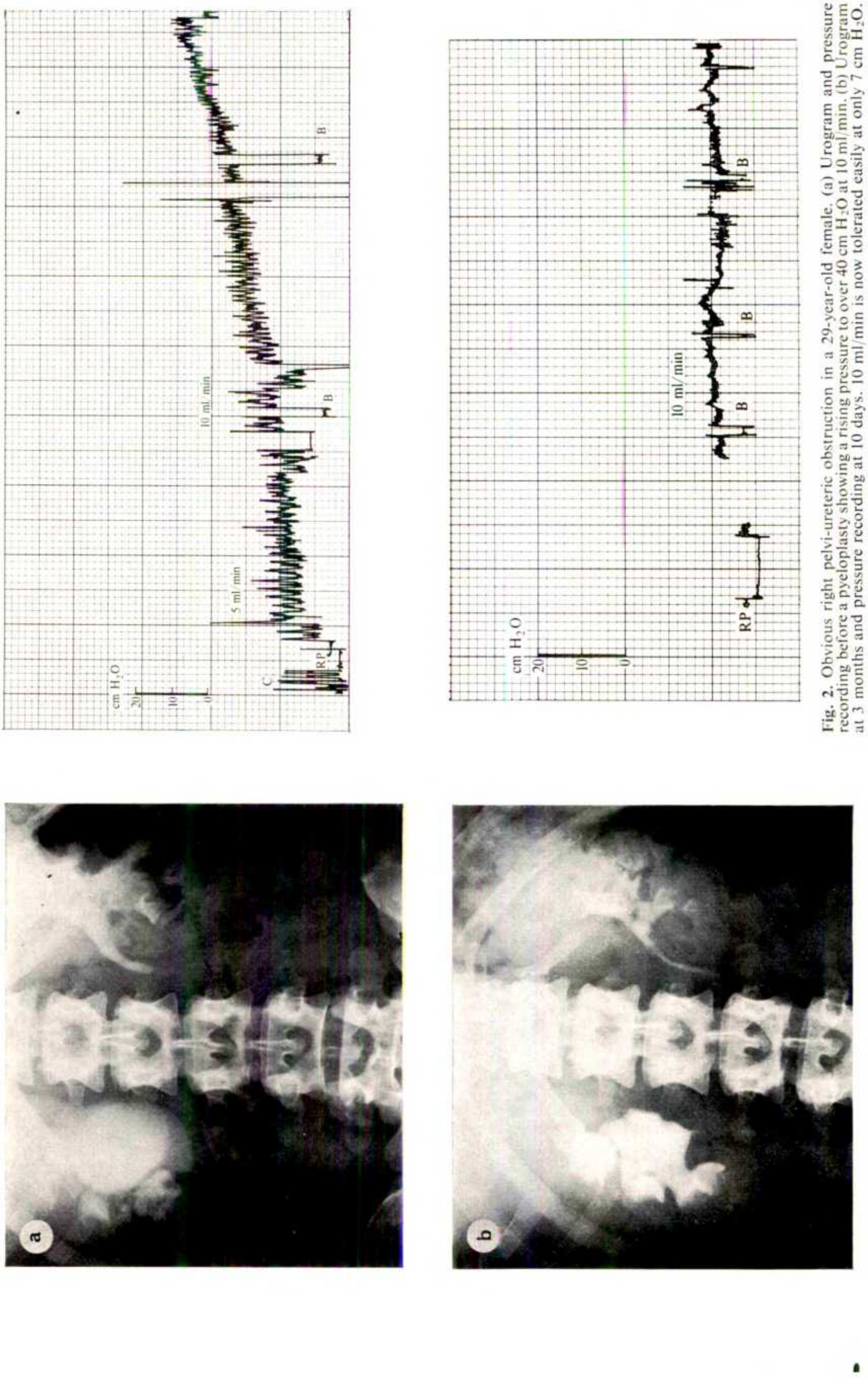
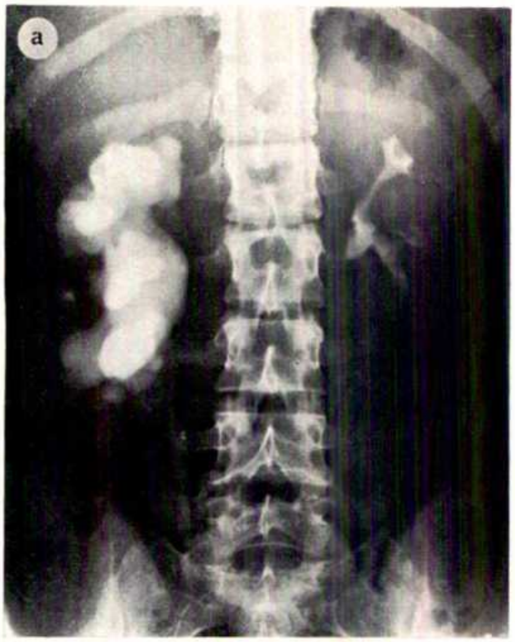
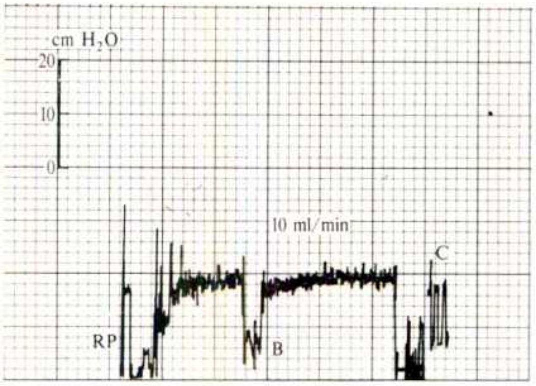


Fig. 2. Obvious right pelvi-ureteric obstruction in a 29-year-old female. (a) Urogram and pressure recording before a pyeloplasty showing a rising pressure to over 40 cm H_2O at 10 ml/min. (b) Urogram at 3 months and pressure recording at 10 days. 10 ml/min is now tolerated easily at only 7 cm H_2O.





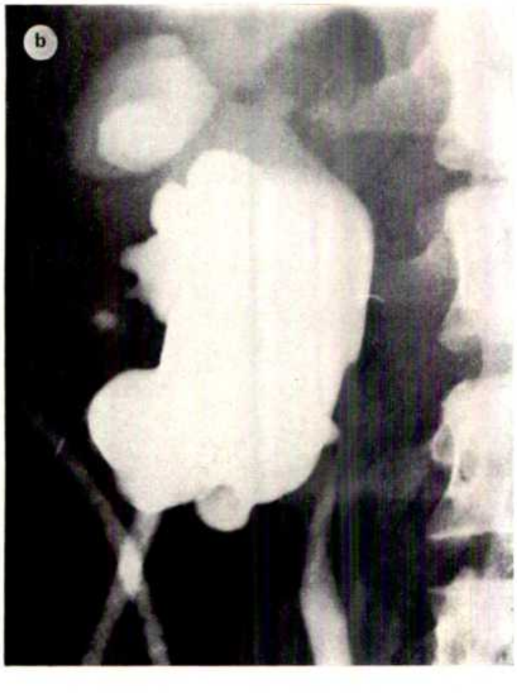
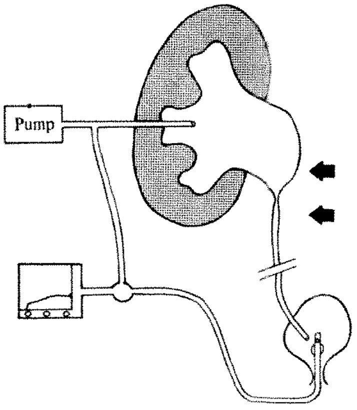


Fig. 3. The problem of equivocal obstruction after pyeloplasty. (a) Urogram of an 18-year-old girl who had had a right pyeloplasty 13 years before. (b) Antegrade pyelogram and tracing showing free flow through the pelviureteric junction at a relative pressure of only 2 cm H_2O at 10 ml/min. This excluded obstruction.

Patients Studied

There are 3 categories of patients. Those investigated at the time of a pyeloplasty for a pelviureteric junction obstruction sufficiently obvious that it would have been performed whether



pressure drop is measured across these points at a simulated diuresis — a perfusion of 10ml/minute.

Fig. 4. Technique of perfusion study. During perfusion of the renal pelvis the pressure is measured in the pelvis and in the bladder to give a relative pressure.

or not the test had been available (19 studies in 10 patients). Those who had previously had a pyeloplasty performed but in whom it was suspected from the clinical and radiographic appearances that all was not entirely satisfactory (5 studies in 5 patients) and, finally, a group of 11 patients (16 studies) who presented with equivocal findings and in whom it was very much in doubt as to whether or not a degree of obstruction was present.

Method

The perfusion study and its application in a variety of obstructive problems has been discussed in detail elsewhere (Whitaker, 1973*a*, *b* and *c*; 1975*a*; Marshall and Whitaker, 1975). Essentially, a single cannula is introduced into the renal pelvis and a fast perfusion of 10 or 5 ml/min is commenced. The back pressure to perfusion and the bladder pressure are measured. The latter subtracted from the former produces a "relative pressure" or pressure drop across the pelvi-ureteric junction at the fixed and steady perfusion rate (Fig. 4).

As judged by the results in over 120 such studies in a variety of conditions both with and without obstruction it seems clear that this relative pressure at 10 ml/min should not exceed 10 to 12 cm H_2O. The apparatus needed for this test is listed in the appendix.

If the decision has been made on clinical and radiographic grounds to perform a pyeloplasty in the certainty that an obstruction is present, clearly such a test is superfluous, but nevertheless a perfusion study with the kidney exposed just before the pyeloplasty produces documented evidence of obstruction and a baseline against which to compare the pressure on perfusing the kidney via a nephrostomy on the 10th postoperative day. Such studies also provide a standard against which the difficult cases can be compared. The cannula or needle is inserted into the renal pelvis away from the pelvi-ureteric junction and before this region is dissected. The kidney is allowed to lie in its natural position.

In the equivocal case the study is performed before, and to help with the decision as to whether or not an operation is necessary. The technique is the same but the cannula is introduced percutaneously under fluoroscopic control after an intravenous injection of contrast medium. It is usually possible to enter the pelvis via a dilated calyx. In the majority of patients, including older children, the procedure is tolerated well under local anaesthesia.

If a low perfusion pressure is found the patient can be discharged from hospital after 24 hours reassured that no pyeloplasty is necessary. If a higher than normal pressure is encountered it is best to drain back the contrast medium via the cannula before withdrawing it and probably wise to advise operation on that admission.

Results

1. Patients with Typical Idiopathic Pelvi-ureteric Junction Obstruction

Perfusion studies were performed on 11 kidneys in 10 patients at the time of pyeloplasty or nephrectomy for this condition. The diagnosis was based on the clinical findings of pain and the typical radiographic appearances of delayed excretion and abnormal accumulation of contrast medium. In the majority of patients a further study was performed via the nephrostomy tube on the 10th postoperative day, 2 days after removal of the ureteric splint.

In all but one of these kidneys there was clear urodynamic evidence of obstruction. The typical finding was the inability of the renal pelvis to tolerate a flow of 10 ml/min without a marked rise in pressure. In 3 kidneys there was an equilibration of pressure at 10 ml/min of between 23 to 36 cm H_2O whilst in 7 others the pressure continued to rise suggesting the pelvi-ureteric junction was completely intolerant of this flow rate (Fig. 2a).

There were lower polar vessels across the ureter in 5 cases and no such vessels in the other 6.

1 patient with a normal pressure had previously had the opposite kidney operated upon after obstruction had been proven by this method. This patient will be discussed, together with details of the other results in this section and the implications of lower pole vessels, in a subsequent report.

On the 10th day after operation perfusion pressures were measured via the nephrostomy tube and they varied between 4 to 16 cm H_2O (mean 10 cm H_2O) in these patients (Fig. 2b).

2. Patients Who had Previously had a Pyeloplasty

Because of the residual dilatation of the pelvis and calyces after a pyeloplasty for chronic pelvi-ureteric obstruction it is often extremely difficult to evaluate the significance of pain and urinary infection occurring sometimes many years afterwards. 5 such patients have been studied. In 1 patient the kidney was explored, found to be thin with a high perfusion pressure (equilibrating at 80 cm H_2O) and was removed.

In a second patient a percutaneous study showed a perfusion pressure of 32 cm H_2O, 10 years after a pyeloplasty. During this time she had undergone 6 intravenous urograms and considerable loin pain. The kidney which was thin was removed and she is now pain free.

A third patient, an 18 year-old girl, had had some discomfort in her right side and a urinary tract infection 13 years after a right pyeloplasty. A plain film showed 3 minute stones in the right kidney and a urogram (Fig. 3a) showed considerable residual dilatation but with good ureteric filling and the stones were in the calyces. A percutaneous antegrade study into this still dilated kidney showed a perfusion pressure of only 2 cm H_2O at 10 ml/min which clearly indicated the absence of any new or residual obstruction (Fig. 3b). She has remained well since without any action being taken.

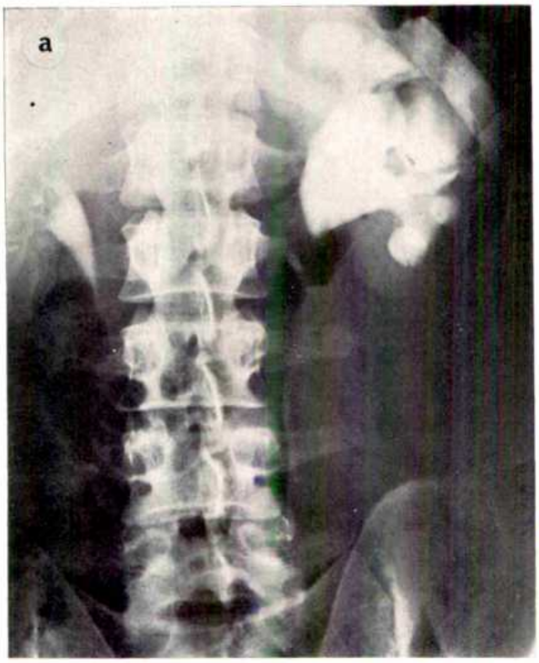
In a fourth patient it was not possible to locate successfully the renal pelvis by the percutaneous method and in a fifth patient, a 9-month-old boy with posterior urethral valves, the study was used to evaluate the upper tract after extensive tapering of the upper ureter together with a pyeloplasty.

3. Patients with Equivocal Pelvi-ureteric Junction Obstruction

These 11 patients presented difficult diagnostic problems and without this test it would have been impossible to be sure that the correct line of management was being taken.

All 11 patients were suspected of having some degree of pelvi-ureteric obstruction. This was confirmed in 5 patients who subsequently underwent operation, whilst in 6 patients normal pressures were found and no action was taken. The subsequent clinical and investigative results in these patients provide no evidence to refute the findings of the tests.

All these patients cannot be described here but 2 examples illustrate the way the results can influence management.



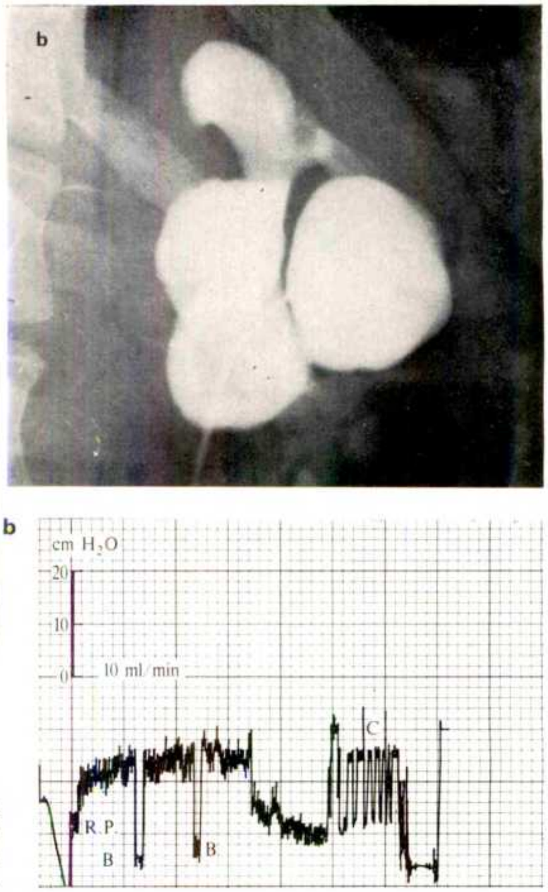


Fig. 5. Equivocal pelvi-ureteric obstruction. (a) Urogram of a 27-year male with left loin pain. Late opacification of the large middle calyx and full pelvis. (**b**) Antegrade and tracing via this calyx showing no hold-up of the medium at the low relative pressure of 7 cm H_2O, excluding obstruction.

Case I

R. P., a 27-year-old teacher had 2 episodes of left loin pain and microscopic haematuria over a period of 1 year before investigation. Plain X-ray showed a few small calculi in both kidneys. No metabolic defect was found. An intravenous urogram (Fig. 5a) showed dilated calyces in the left kidney with a full pelvis. The middle calyx was large and opacified poorly in the early films. A percutaneous antegrade pyelogram was performed (Fig. 5b) which showed good flow through the pelvi-ureteric junction and satisfactory emptying of the distended calyx into which the cannula was inserted at a low pressure of 7 cm H_2O. The patient has had no further pain but as a result of this test we were able to reassure him that, although the stones may give more trouble, if they eventually needed to be removed it would not be necessary to pay any surgical attention to the hydrocalicosis or pelvi-ureteric junction in terms of obstruction. As he spent much of his time travelling we felt this was important information for him to pass on if he was admitted.

Case II

G. B., an 11 year old boy had a left pyeloplasty performed 3 years previously for a definite pelvi-ureteric obstruction. It was noted at that time that the right calyces and renal pelvis were full and that this right side would need watching carefully in case it, too, developed an acute hydronephrosis (Fig. 1).

A further urogram (Fig. 6a) showed a satisfactory result on the left side but persistent abnormality on the right although the ureter appeared to fill well. A percutaneous antegrade study (Fig. 6b) showed a narrow area at the pelvi-ureteric junction and the pressures confirmed that this represented a significant degree of obstruction. The relative pressure at both 10 and 5 ml/min was 25 cm H_2O.

This child has now had a right pyeloplasty. At operation the renal pelvis rapidly became tense with a perfusion of either 5 or 10 ml/min and the ureter showed poor attempts at peristalsis. A further perfusion study at that time confirmed the obstruction. A Culp type of pyeloplasty was performed and a pressure controlled nephrostogram at 10 days showed good drainage at a pressure half the preoperative level.

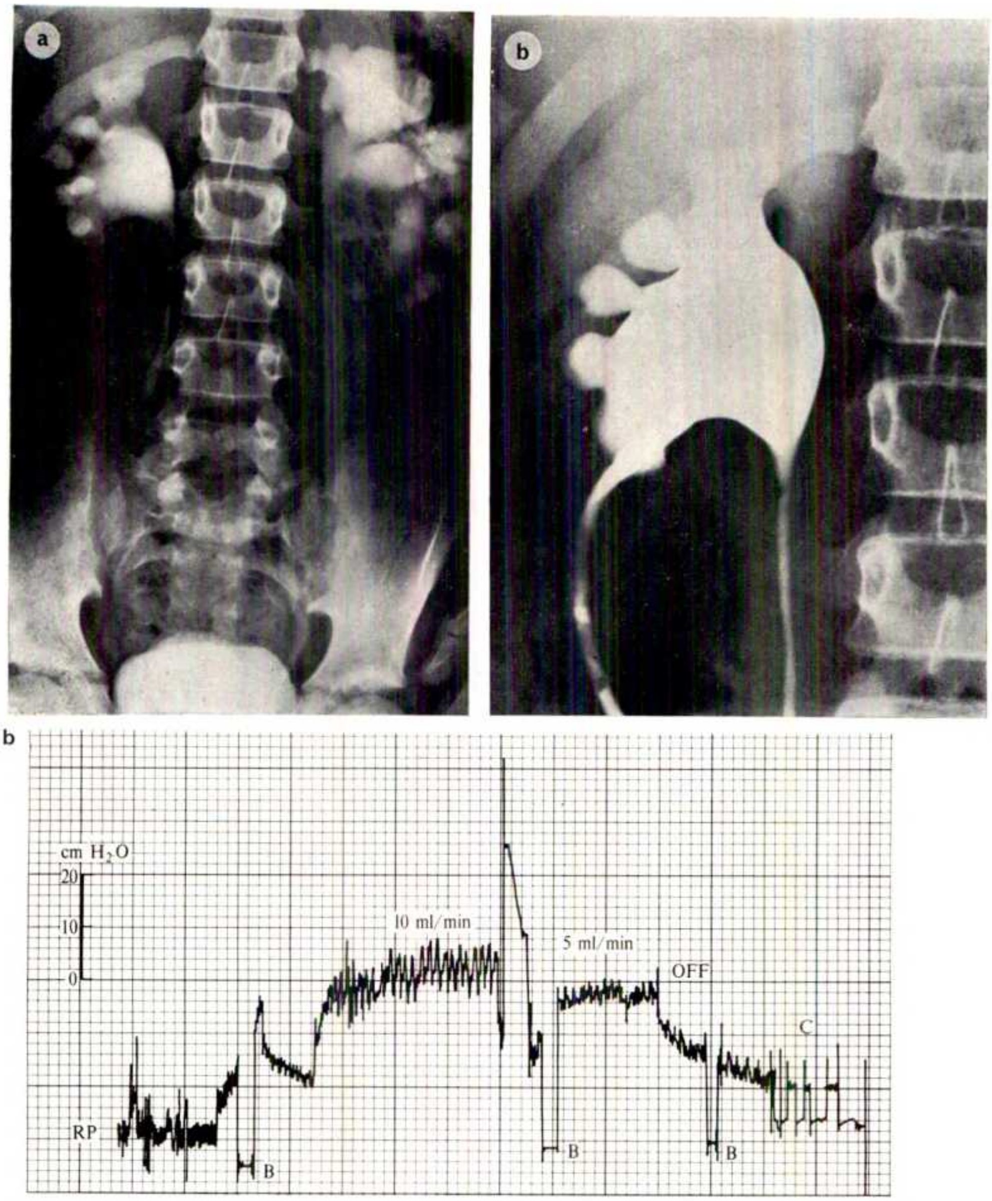


Fig. 6. Equivocal pelvi-ureteric obstruction. An 11-year-old boy who 3 years previously had a left pyeloplasty for marked hydronephrosis. The right pelvi-ureteric junction had always been under suspicion (Fig. 1 shows a previous urogram). (a) Urogram 3 years after left pyeloplasty. (b) Antegrade and tracing. Definite and constant narrowing at the pelvi-ureteric junction and study shows a relative pressure of 25 cm H_2O at both 5 and 10 ml/min. This is a moderate obstruction.

Discussion

These cases and others which have not been fully described illustrate the usefulness of this perfusion test in diagnosing obstruction in difficult situations.

The obvious advantage of showing an obstruction is that an operation can be advised early before there is further deterioration in renal function. If the system can be shown to be unobstructed the patient can avoid multiple clinic attendances and unnecessary X-rays with the inevitable time off work and loss of earnings.

Morbidity has consisted of 1 instance of haematuria with clot colic and 2 instances of pain for 24 hours from extravasation of contrast medium. With improved technique we feel that these problems can be minimised.

The test requires the minimum of equipment (see appendix) and understanding of urodynamics, but for the percutaneous studies good radiological help and a suitable cannula are essential.

In the light of these results the radiographic appearances of pelvi-ureteric obstruction need some reconsideration and the technique provides a control for the estimation of obstruction by radio-isotopic methods which to date have been disappointing in the equivocal cases. The findings have also helped the author to understand the mechanisms of obstruction in the pelvi-ureteric region (Whitaker, 1975*b*).

Summary

A series of 40 studies have been used to assess whether or not there is obstruction in the pelvi-ureteric region in 27 kidneys. The perfusion test which is discussed has provided an answer in all cases where the technique was possible and allowed a logical decision to be taken concerning management.

4 of the equivocal cases were patients under the care of Mr J. F. R. Withycombe and I am grateful to him for allowing me to study them.

Appendix

For those who wish to perform a perfusion the following list of equipment may be helpful. It is appreciated that most of the equipment is probably available from several manufacturers but those listed have been used by the author and found satisfactory.

Basic Equipment

1. *Perfusion Pump* (Braun (acc 71104) with autoclavable 50 ml luerlocking syringe (acc 72465)).
2. *Pen Recorder* (Smiths Servoscribe 1 channel (RE 501.20)).
3. *Physiological Pressure Transducer* (Statham P23 Db.).

Disposable Sterile Equipment

The following items are needed for each test:

1 4-way stopcock. (Baxter BR 62s).
2 3-way stopcocks. (Pharmaseal K75a).
1 wide-bore extension set (Avon-A60).
1 200 cm manometer line (Portex 200/490/200).
2 60 cm manometer lines (Protex 200/490/060).
1 male-to-male connector for connection between the urethral catheter and the apparatus. (This can be made using a small length of silastic tubing and two male connectors.)
1 bottle of glycerine or liquid paraffin to lubricate syringe.
1 bottle of saline or contrast medium (30% Urograffin) for perfusion.
1 cannula—hondwel Catheter (Teflon) (Becton, Dickinson & Co. 18.G. 6″ or 4″).

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A Simple Classification of Wide Ureters

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There can be few topics in urology which are more confused or confusing than that of the abnormal ureter. As a result, rational discussion on the management of such lesions is almost impossible unless it is made quite clear which abnormality is present.

Efforts have been made to classify abnormal ureters but generally they have failed to clarify the situation because they have been either too simple or unnecessarily complex. Also, the basic distinction between the refluxing and the non-refluxing ureter has often been ignored.

We wish to discuss the problems of classifying ureters in the light of the numerous efforts reported in the literature and to set out an alternative classification which hopefully incorporates the best features of some of them and at the same time excludes the confusing aspects. We feel it is time for a classification which is internationally acceptable.

The Problem

3 factors make a new classification desirable. Firstly, there are now too many terms which convey different pathological entities to different observers (Fig. 1). Secondly, the need to distinguish between a refluxing and a non-refluxing ureter has been highlighted by the increasing and now well established awareness of the problems of reflux. Thirdly, a newer concept, but of paramount importance in terms of management, is the need to diagnose accurately the presence or absence of obstruction in the wide non-refluxing ureter.

It is not our intention to criticise all previous attempts at classification but it is necessary to analyse some aspects of them to rationalise a new approach.

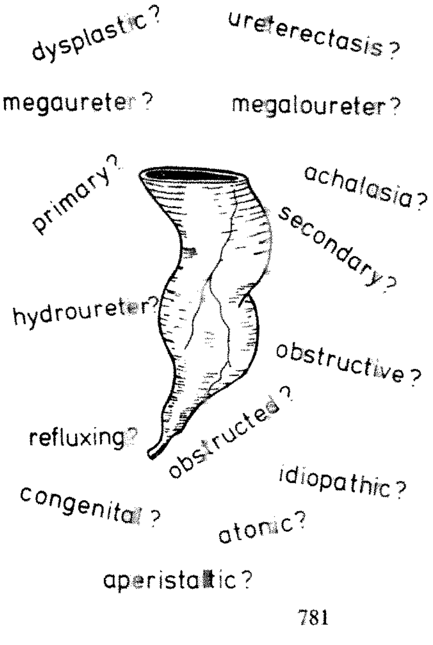
dysplastic?
ureterectasis?
megaureter?
megaloureter?
primary?
achalasia?
secondary?
hydroureter?
obstructive?
refluxing?
obstructed?
idiopathic?
congenital?
atonic?
aperistaltic?

Fig. 1. The problem.

For instance, in his text book, Campbell (1970) discusses the *Primary Megaloureter* as an example of congenital dilatation of the upper tract and lists possible aetiological factors. He accepts, rightly in our opinion, that not all such ureters are obstructed but suggests that reflux is usually present. Hence, he is using this term for too large a group of abnormal ureters which includes both the refluxing and non-refluxing types. Hinman (1970) prefers the term *Hydroureter* for the wide non-refluxing ureter and argues that all dilatation of the ureter is due to obstruction. We would beg to differ with this view.

Many early classifications are much less specific and give two broad categories of *congenital* and *acquired* aetiologies. Others (Culp, 1967) make a distinction on anatomical or embryological lines.

Williams (1970) provides a realistic approach. He distinguishes clearly between refluxing and non-refluxing ureters and then categorises the wide non-refluxing ureter into groups according to the following pathogenic factors:

Polyuria;
Bacterial toxins;
Obstruction (stricture, atresia, associated saccule);
Obstructive megaureter;
Dilated ureter with bladder outflow obstruction;
Dysplasia with or without renal impairment.

Although this classification has much to recommend it, it fails in the light of present knowledge to clarify the group of what Williams calls (*Primary*) *Obstructive Megaureters* (Williams and Hulme-Moir, 1970; Williams, 1974). The word *obstructive* suggests that it is the ureter, perhaps because of its width, which causes the obstruction and indeed this may sometimes be the case (Whitaker, 1975) but many feel that the dilatation is due to an abnormal lower ureteral segment in which case the term should be *obstructed* ureter.

However, more important is the fact that the concept of obstruction is used too loosely in connection with this type of ureter. This is not just a quibble with the nomenclature but has a major clinical implication now that obstruction can be accurately assessed (Whitaker, 1973). Having used the expression *Primary Obstructive Megaureter* Williams begs the question of its usage by quoting his own findings of occasional spontaneous improvement in the appearances of such ureters with conservative treatment only (Williams and Hulme-Moir, 1970). He also accepts the findings of Bäcklund and Reuterskiöld (1969) that low ureteric pressures may sometimes be demonstrable on perfusing such ureters. Both these findings are incompatible with a significant degree of obstruction. Furthermore, Heal (1973), using the same unfortunate term—*Primary Obstructive Megaureter*—showed that in 10 of 15 adults the pyelographic appearances remained unchanged, a feature again incompatible with a significant degree of obstruction.

This suggests that *Wide non-refluxing* ureters come in varying degrees of obstruction. Those presenting early in life are naturally more likely to be obstructed. Johnston (1967), who termed these ureters *Functionally Obstructed Megaureters* found considerable improvement following re-implantation in children whilst Heal (1973) was seeing adults at the other end of the range with very mild or absent obstruction.

Belman's classification (1974) fails to distinguish adequately between the obstructed and non-obstructed "primary megaureter" and some authors (Hodgson and Thompson, 1975) are still erroneously stating that "megaureters" are either refluxing or functionally obstructed and ignore the concept of a non-obstructed, non-refluxing wide ureter.

Finally, there is the problem of confusing terms. This is often because attempts are made to indicate the aetiology of the defect as well as an anatomical description. The word *dilated*, for instance, implies that the ureter was once of normal calibre, which is clearly not always so as in the prune belly or megaureter-megacystis syndromes. The term *Hydroureter* has little to recommend it and to some it implies a high pressure within it. *Megaureter* has been used for so many

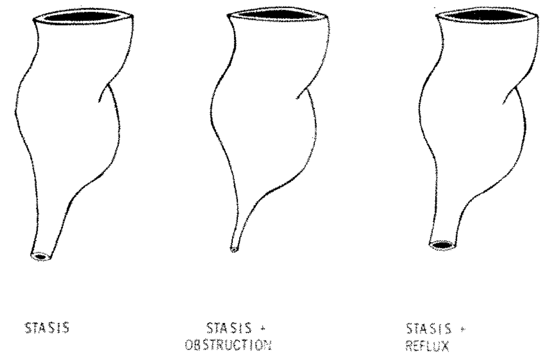

Fig. 2. The 3 possible complicating factors in wide ureters.

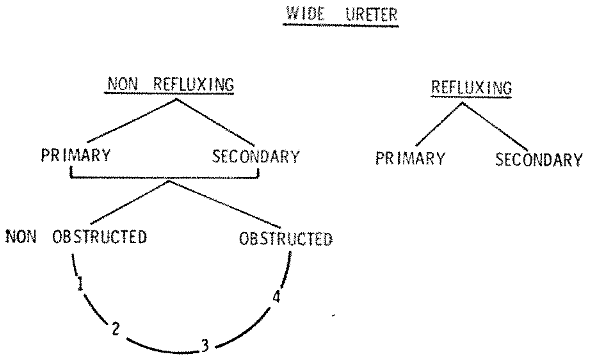

Fig. 3. The proposed classification. The numerals indicate an empirical range of degrees of obstruction.

conditions with and without reflux and bladder outflow obstruction that it cannot now be usefully salvaged for a new classification. *Primary* and *secondary* are important terms and need careful definition.

It is with this background of confusion that the following classification is proposed.

A New Classification

The term we believe to be the most acceptable for an abnormally wide ureter is simply *wide*. The purely descriptive term suggested by Bäcklund and Reuterskiöld (1969) is anatomically and radiographically accurate and makes no effort to indicate the aetiology.

The clinical implications of such a wide ureter are threefold (Fig. 2). First to be considered is the problem of stasis alone. In the absence of reflux or obstruction the mere presence of a large volume of urine in the upper tract may lead to repeated or continuous infection. Ureteritis appears to be an important factor in causing the ureteric widening often seen when there are infected stones in the renal pelvis; following removal of the stones and elimination of the infection the ureter promptly returns to normal.

Secondly, there is the problem of obstruction which will lead not only to stasis with its risks of infection but also to back pressure on the kidney and deterioration in renal function. Thirdly, reflux may be present and the consequences of this are well known.

It is on these 3 factors that the classification is based (Fig. 3).

Firstly, wide ureters either show or do not show vesico-ureteric reflux and from the point of view of management we consider this distinction to be of paramount importance, although Hendren (1975) believes otherwise. It is often implied and indeed has been repeated recently (Hodgson and Thompson, 1975), that if a wide ureter is not showing reflux then it must be obstructed; this is a misconception which is hard to dispel.

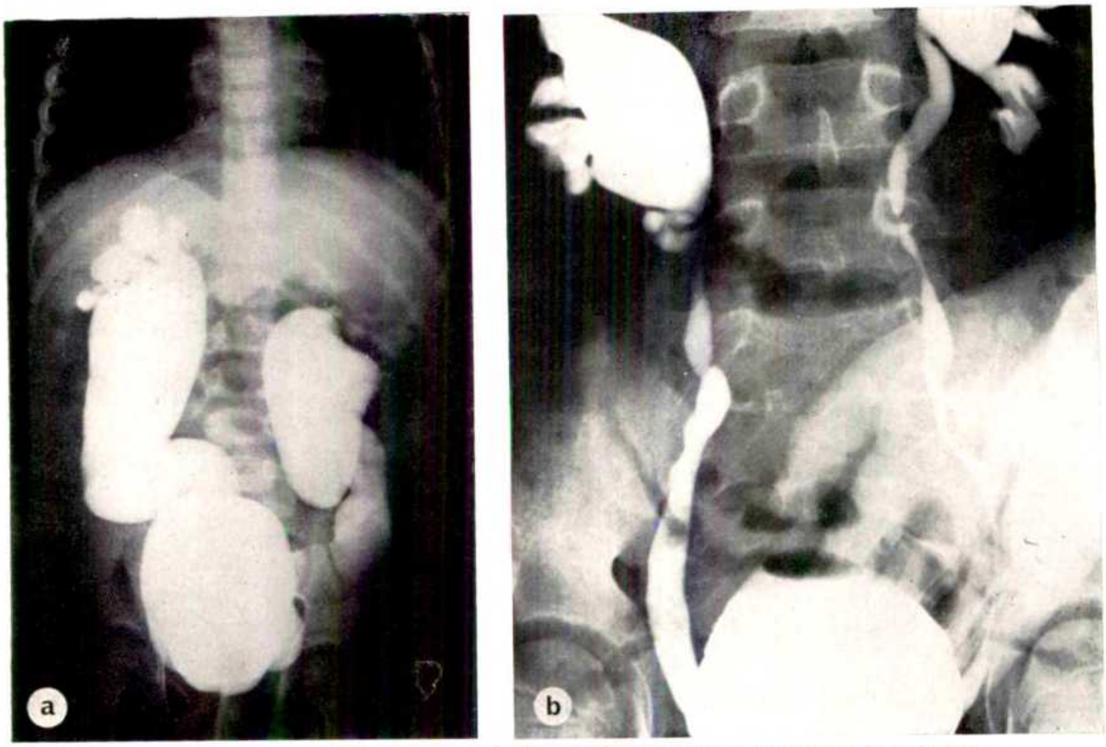

Fig. 4. Primary refluxing ureters. (a) Massive neonatal reflux, (b) the more usual type of reflux (cystograms).

Secondly, the 2 groups of refluxing and non-refluxing ureters can be subdivided into *primary* and *secondary*. The term *primary* is used if the bladder functions effectively at normal pressures. If reflux is present such ureters can be conveniently subdivided into the massively refluxing type seen usually in the neonatal period (Fig. 4a) or the more conventional and less dramatic type of reflux seen in children of a much wider age group (Fig. 4b). A third category of primary reflux would include ureters in patients with a general dysplasia of the urinary tract such as the prune belly or megacystis-megaureter syndromes.

Secondary means that there is, or has been a temporary or permanent high pressure in the bladder which has either caused or exacerbated the abnormality of the ureter. The most obvious example of this is the wide ureter which is seen with prostatic obstruction in men or with urethral obstruction in young boys with posterior urethral valves. In either situation reflux may be present and is probably caused by a "blowing-out" of the uretero-vesical junction by the high pressure within the bladder. Ureteric dilatation then occurs by the transmitted intravesical pressure.

Alternatively, the uretero-vesical junction may retain its competence but the high pressure within the bladder may make it difficult for the ureter to empty and the result again is an increase in the width of the ureter.

The final distinction in the classification is whether or not obstruction is present at the uretero-vesical junction. It is this factor and the difficulty until recently in making a definite diagnosis of obstruction in a wide upper tract which has led to most of the confusion. We have already suggested that not all wide, non-refluxing ureters are obstructed and from a clinical management point of view it is all important to make this basic distinction. It cannot be overemphasised that unnecessary operations undertaken on the mistaken assumption that an obstruction exists are fraught with danger and disappointment.

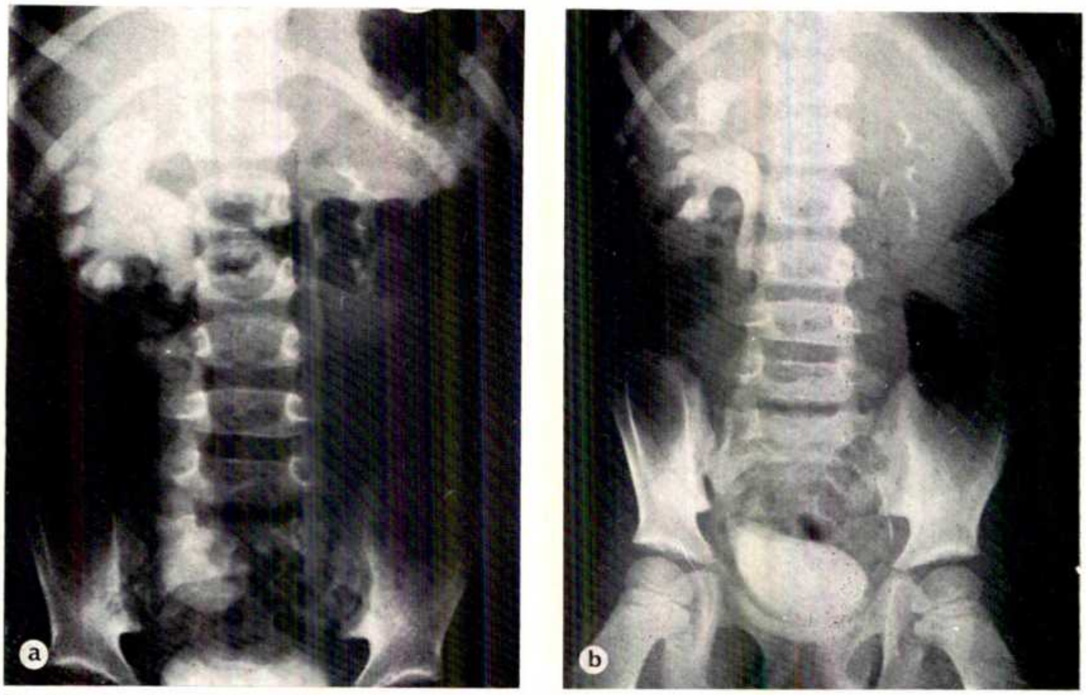

Fig. 5. Primary obstructed non-reflexing wide ureter. Intravenous urograms showing wide right ureter. (a) Before operation, and (b) 1 year after tapering and re-implanting.

Obstruction in the wide non-refluxing ureter, if present, can be due to primary or secondary causes as defined above. For instance, a defect in the uretero-vesical junction which prevents adequate emptying in the presence of a normal bladder is termed *primary* (Fig. 5a and b). This ureter has been termed primary (idiopathic), obstructed(ive) megaureter. More accurately, if rather more cumbersomely, it should be termed a *primary obstructed, non-refluxing wide ureter*. Although long-winded there is no doubt what is meant by this term.

If the outflow from the bladder is obstructed either functionally, as in a neurogenic bladder, or anatomically, as in prostatism or posterior urethral valves, there is usually no actual obstruction at the uretero-vesical junction and relief of the bladder outflow obstruction will lead to resolution of the upper tract dilatation (Fig. 6a and b). This is a *secondary non-obstructed, non-refluxing wide ureter*. However, sometimes there can be such hypertrophy of the detrusor around the intramural ureter that even after relief of the raised bladder pressure the ureter still cannot drain satisfactorily. This is termed *secondary* obstruction and the ureter is a *secondary obstructed, non-refluxing wide ureter*. If after resection of posterior urethral valves there is a deterioration in urographic appearances or renal function this type of ureter is suspected but it is a simple matter to prove it with a perfusion test.

The term *secondary* must be kept strictly for the ureter associated with an "obstructed" bladder and not used for compression of the ureter by vessels, tumour or stone.

Obstruction is, of course, relative and we suggest that there is a whole range of non-refluxing ureters which are variously obstructed from almost not at all to grossly and it is in this grey area of equivocal obstruction that the perfusion (pressure/flow) studies are so helpful (Whitaker, 1973).

This classification can be extended to include any type of abnormal ureter although this can easily become an academic exercise and of limited clinical applicability.

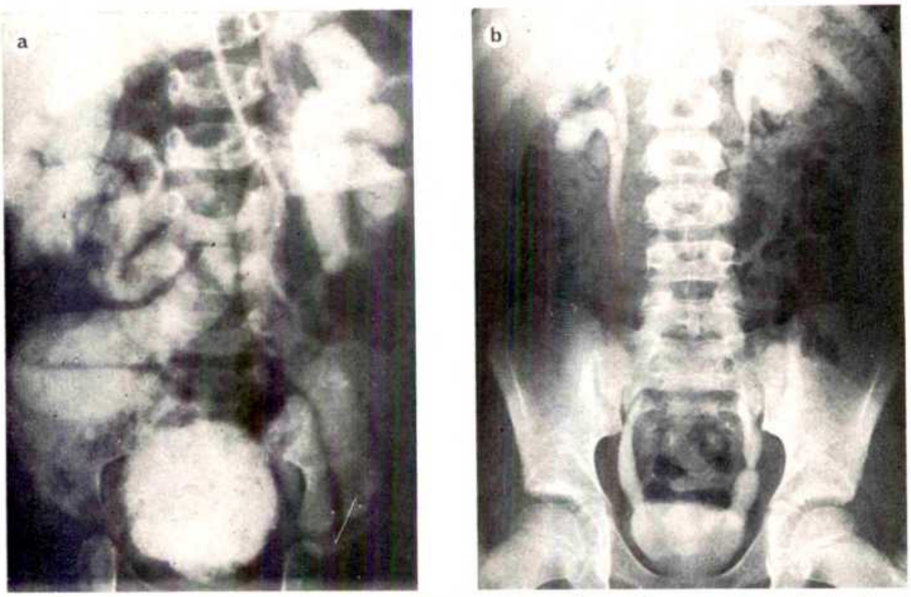

Fig. 6. Secondary non-obstructed non-refluxing wide ureters. Boy with posterior urethral valves treated by endoscopic resection of valves only. Intravenous urograms. (a) At age 4 months, before operation. Cystogram showed no reflux. (b) At age 9 years. There has been considerable spontaneous improvement in the dilatation and tortuosity of the ureters incompatible with a significant degree of uretero-vesical obstruction.

The main usefulness of this classification is in distinguishing between the various types of congenital anomalies which are seen so commonly in children and its adoption should see an end to many of the confusing terms such as megaureter, megaloureter, hydroureter and at least 10 other obsolete terms listed by Belman (1974).

Summary

A simple classification of abnormal ureters is presented which categorises the ureters according to the presence or absence of 3 factors, namely reflux, bladder outlet obstruction and ureteric obstruction. It has been devised to try to rid the literature of many confusing and obsolete terms and it is hoped that this new classification may become internationally accepted.

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Ring Ureterostomy

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The management of the congenitally obstructed urinary tract with gross dilatation of the ureters in infancy presents formidable metabolic and technical problems. It is generally agreed that the immediate treatment must be concerned with correction of dehydration and electrolyte disturbances, together with decompression of the urinary tract and treatment of infection. Thereafter there will be many cases in which a simple surgical correction of the primary obstruction, often urethral valves, will suffice; there will be others in which the infant's condition requires and permits that there should be an early remodelling and reimplantation of the ureters as well as elimination of the obstruction. There will remain a few, however, in which renal failure, severe infection, incompetence of ureteric peristalsis and a poor general nutritional state make immediate reconstructive ureteric surgery hazardous. It is for these that a tubeless upper urinary tract diversion, which can be maintained for some weeks or months but which can be replaced, may be beneficial. When cutaneous ureterostomy was first introduced the immediate benefit in such infected uraemic infants was evident and a great many such operations were performed, sometimes inadvisedly, and only later were the disadvantages of the procedure better understood. A suitable procedure should fulfil the following requirements:

1. Effective drainage should be easily established to allow improvement of renal function and recovery of ureteric peristalsis.
2. No indwelling tubes should be required, since these may perpetuate infection as well as posing a management problem.
3. The ureteric blood supply must remain intact to provide stomal viability and prevention of stricture.
4. Some pathway for urine flow to the bladder should remain, thereby obviating complete defunctionalisation with its potential for vesical contracture.
5. The procedure should be fully reversible by a simple closure method which will not interrupt ureteric continuity or interfere with subsequent re-implantation of ureters into the bladder.

The Johnston (1963) skin bridge loop ureterostomy rarely has any problem of stomal stenosis but requires excision of the exteriorised loop and end-to-end anastomosis for closure. The Perlmutter and Tank (1968) loop ureterostomy, in which the loop of ureter is brought to the skin incision and opened without a bridge of muscle, is more liable to stomal retraction and stenosis and although ureteric continuity can be restored without excising any length of ureter, subsequent stricture may occur. In both these forms of diversion there is also little or no urine flow down the distal limb of the ureter; this has the risk of allowing bladder contracture as well as posing problems in ureteric re-implantation in a dry field.

Cutaneous pyelostomy, rotating outwards a very grossly dilated renal pelvis, is only suitable for a small number of cases and again the stoma is apt to retract.

The Sober (1972) Y ureterostomy permits decompression and passage of urine into the bladder at the same time but the stoma is an end one and is apt to stenose. Ghazali (1974) reported gangrene in 1 of 9 cases of Y ureterostomy and stomal stenosis in others. Overall, end cutaneous ureterostomies are liable to stenosis as reported in 39 out of 62 cases by Eckstein and Kapila

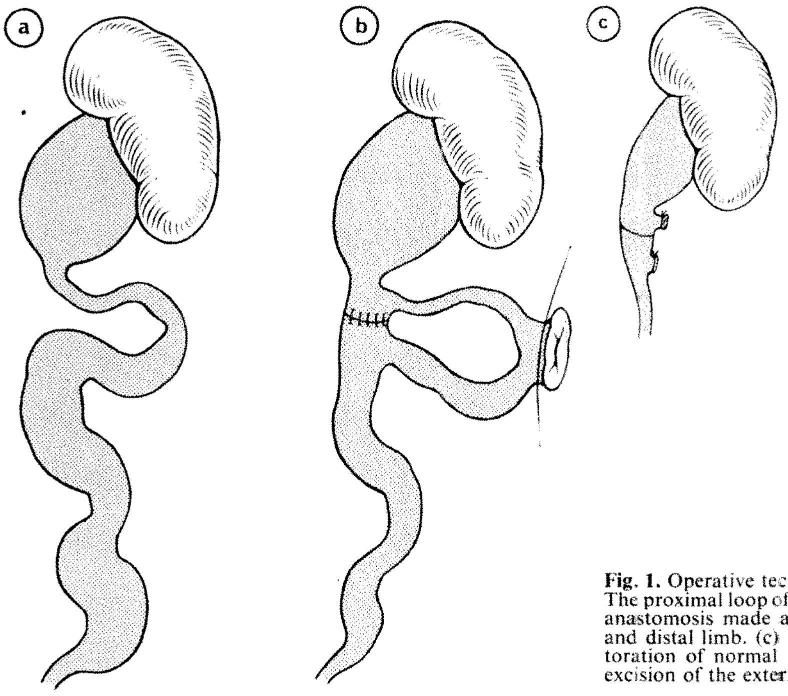

Fig. 1. Operative technique for ring ureterostomy. (a) The proximal loop of dilated ureters drawn out. (b) An anastomosis made at the base between the proximal and distal limb. (c) After renal recovery an easy restoration of normal ureteric continuity is effected by excision of the exteriorised arc.

(1970). This complication underlines the importance of maintaining vascular continuity and the advantages of the loop form of ureterostomy.

To overcome the difficulties of present methods and to fulfil the criteria outlined we now describe a technique of ring ureterostomy, which combines the advantages of the loop and the Y ureterostomy.

Technique

The child is placed in the flank position and a short skin incision is made below the 12th rib, rather anteriorly. The muscles are divided and the retroperitoneal space entered. The ureter, which must be large and tortuous for the technique to be suitable, is identified without difficulty. The highest loop of ureter is chosen and traced up to the renal pelvis, care being taken not to devascularise it, while freeing proximally obstructing kinks (Fig. 1a). Following mobilisation the loop of ureter to be used should be drawn out of the wound by a rubber sling, and an anastomosis made between the 2 limbs of the loop at the base. 2 longitudinal ureterotomy incisions are made, approximately 2 cms in length parallel to one another in the proximal and distal limbs and a side-to-side anastomosis is performed with 0000 continuous Dexon suture. Often it is convenient to employ the renal pelvis itself to form the upper limb, thus effectively performing a pyeloplasty in cases with secondary pelvi-ureteric obstruction due to kinking. A ring of ureter is thus created, the superficial arc of which is brought out through the incision and the muscle layer is closed in a bridge through the centre of the ring. The exteriorised arc is then incised laterally and sutured to the skin (Fig. 1b). The absence of kinks may be confirmed by the passage of a catheter but no indwelling tube should be required. The operation can be performed bilaterally at the same session.

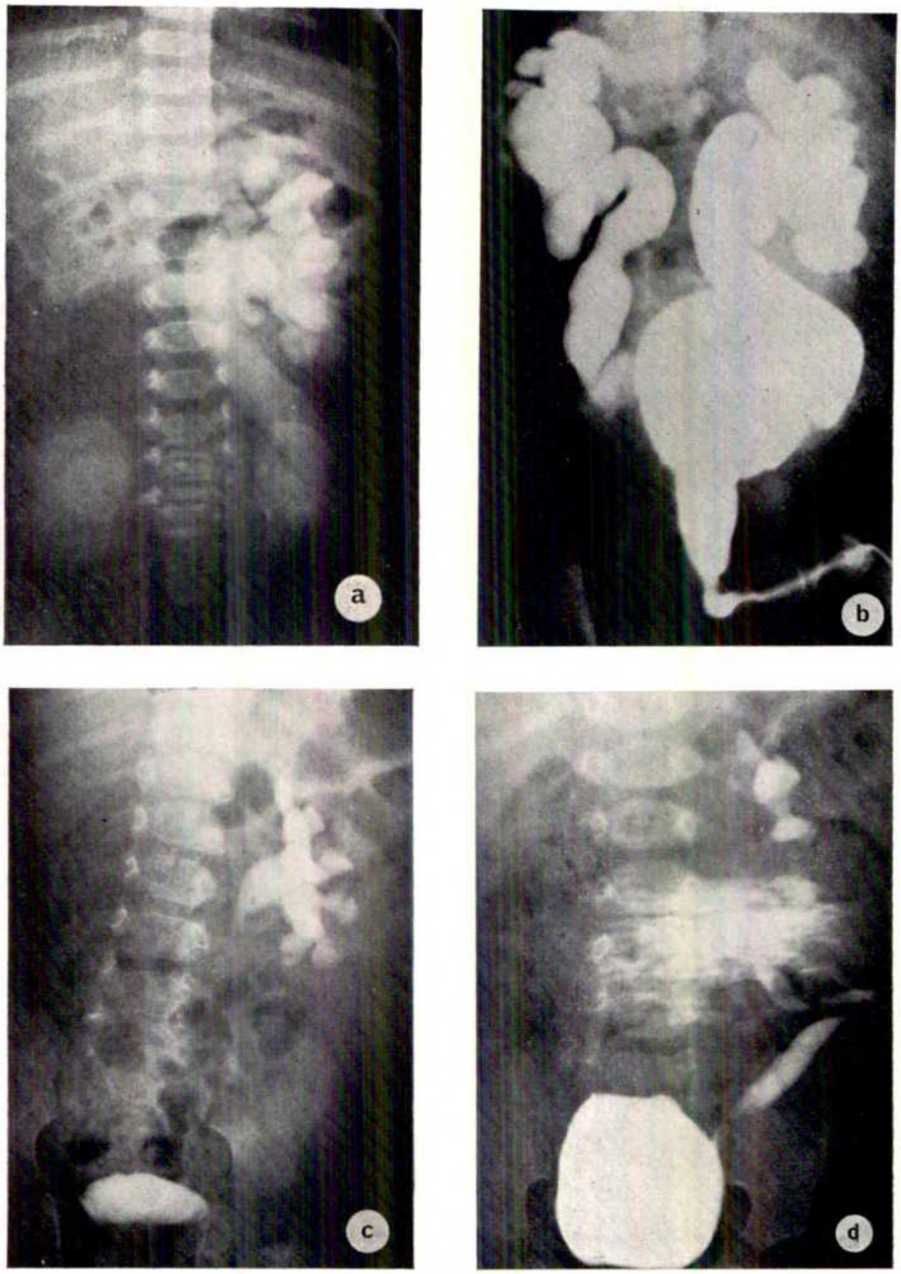

Fig. 2. Treatment of upper tract dilatation in urethral valves by ring ureterostomy. (a) Intravenous pyelogram in a uraemic infant with chronic retention. No function on the right side, gross dilatation on the left. (b) Cystogram in the same child. The right kidney proved to be functionless and was removed. (c) Intravenous pyelogram 6 months after left-ring ureterostomy demonstrating restoration of a satisfactory pyelogram on the left side but also filling of bladder through the ring anastomosis. (d) Cystogram in the same child showing persistent left reflux but a normal calibre ureter, subsequently reimplantation of the ureter with ureterostomy closure was completed.

Following healing, the superficial loop easily maintains its viability and drains urine satisfactorily, but the passage of some urine to the bladder continues. After some months have elapsed it is likely that both renal function and ureteric peristalsis will have improved so that closure should be possible. However, re-implantation of the lower end of the ureter may be required because of secondary obstruction or reflux and this can be undertaken without interfering with the ureterostomy. At the time of closure the stoma is circumcised, the loop mobilised, the proximal and distal limbs excised down to the site of anastomosis leaving the ureter in continuity with only a lateral suture line (Fig. 1c).

Clinical Experience

10 ureterostomies have been performed on 7 male infants and 4 of them with posterior urethral valves, 3 with the prune belly syndrome in its complete or incomplete form. All children had severe renal impairment with massively dilated collecting systems and evidence of secondary uretero-vesical junction obstruction or reflux (Fig. 2). 4 of the 6 were infected preoperatively, 2 with significant septicaemia and 1 with multiple ureteric calculi. All drained satisfactorily and the urine became sterile but in no case was the bladder completely isolated. Closure has so far been effectively undertaken in 4 cases and others are awaiting closure.

Summary

A method is described for temporary cutaneous ureterostomy which combines the advantage of loop ureterostomy with a well vascularised stoma with those of the Sober Y operation allowing easy restoration of ureteric integrity.

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Acute Urinary Retention in the Female

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A review of the literature reveals little about the incidence and aetiology of acute urinary retention in the female. Traditional textbook opinion would suggest that it is a very rare phenomenon, the commonest causes being gynaecological problems, neurogenic bladder and hysteria.

An originally retrospective and subsequently prospective survey was undertaken in the Bristol Clinical Area in the years 1972, 1973 and 1974 in an attempt to uncover the true incidence and aetiology of the condition. The criteria for inclusion in the survey were that the retention was painful, acute in onset and that on catheterisation less than 1 litre of urine was obtained. These strict criteria were used in order to exclude doubtful cases of chronic retention.

Despite the rigid application of the criteria defined above and the difficulties involved in collecting cases from several centres the survey revealed 103 cases. After exclusion of those occurring postoperatively (25) and post-partum (33) there were 45 cases, all of whom had been admitted to hospital because of their retention. These cases fall naturally into 5 groups when considering the causes of the retention (Table I) and these groups have been analysed in further detail.

Table I

Aetiology of Acute Urinary Retention in 103 Female Patients in Bristol Clinical Area 1972-74

Cause		No. of patients
Postoperative		25
Post-partum		33
Others		45
1. Gynaecological	17	
2. Urological	15	
3. Neurological	7	
4. Psychiatric	3	
5. Rectal	3	

Gynaecological

The importance of intrapelvic tumours as causative agents in acute urinary retention has been stressed previously (Ward, Lavengood and Draper, 1968) and is confirmed in this series (Table II).

The diagnosis will usually be obvious if a thorough pelvic and bimanual examination is performed and this is therefore essential. A pelvic mass causes retention either by exerting extrinsic pressure on the bladder neck or urethra, or by overstretching these structures, and the same mechanisms are probably responsible for retention, secondary to procidentia and vulval haematoma All the patients in this group recovered normal micturating habits following treatment or resolution of the precipitating factor.

Table II

Gynaecological Causes

Cause		No. of patients
Pelvic mass	Fibroids	5
	Gravid retroverted uterus	4
	Retroverted uterus	2
	Ovarian cyst	1
	Pessary	1
Procidentia		2
Vulval haematoma		2

Urological

15 patients were judged to have retention secondary to abnormalities in the urinary tract (Table III).

At endoscopy, 7 were found to have definite obstructive lesions—2 believed to be at the bladder neck and 5 in the urethra. The diagnosis of bladder neck obstruction in the female is difficult but in both these patients the acute urinary retention was associated with a normal calibre urethra, a trabeculated bladder and in each case responded dramatically to transurethral resection of the bladder neck.

A further 7 have been classified as inflammatory and these all had heavily infected urine on presentation. At endoscopy, 5 of these had trabeculation of the bladder wall and a 6th had a normal lower tract. 1 patient was not endoscoped.

The one iatrogenic case was a woman in whom a gracilis sling had been fashioned.

Return to normal micturition was obtained following resection of the bladder neck in the cases with obstruction at this level. The patients with urethral stenoses underwent urethral dilatation and were less successfully treated, in that 4 out of the 5 have required subsequent dilatation. Antibiotics were given to the inflammatory group and all were able to micturate normally following removal of the urethral catheter. None of this group has required further treatment. The woman with the gracilis sling has subsequently had urinary diversion into an ileal conduit.

Neurological

The presence of 7 cases in this group (Table IV) underlines the importance of full neurological assessment of the patient presenting with acute urinary retention.

Table III

Urological Causes

Cause		No. of patients.
Obstruction	Bladder neck	2
	Urethra	5
Inflammatory		7
Iatrogenic		1

Table IV

Neurological Causes

Cause	No. of patients.
Disseminated sclerosis	2
Traumatic paraplegia	1
Sacral agenesis	1
Cerebral metastasis	1
Parkinsonism	1
Senile dementia	1

In only 2 cases was the neurological condition known to exist at the time of presentation. Considerable concern is caused by the initial diagnosis of "hysterical retention" in 2 of the patients in this group. The dangers inherent in the placing of a label of hysteria on females with urinary retention have been forcibly commented on by previous authors (Emmett and Love, 1968; Ivanovici, 1970) and are again found to be very real. It is also of interest that these neurological lesions can produce an acute as well as a chronic urinary retention.

Psychiatric

In 3 patients no organic cause was found for the retention of urine despite thorough general, pelvic and neurological investigation. 2 of these patients were children with profoundly disturbed home backgrounds and the third was a woman of 56 years with severe endogenous depression. All three underwent management in psychiatric units and have had no further episodes of urinary retention.

Rectal

There were 3 patients in this group. 2 had faecal impaction while the third was suffering from severe colitis. None have suffered a second episode of retention. Faecal impaction is well recognised as a cause of retention in the male but may also produce this effect, though much less commonly, in the female.

Summary

The causes of acute urinary retention in the female are discussed in relation to 103 cases recorded over a 3-year period.

The authors feel that the findings are at variance with traditional teaching on the subject. Rather than being very rare the condition is found, in fact, to be not uncommon. It is found to occur postoperatively and following childbirth. Gynaecological and neurological lesions are reaffirmed as important causes and pathology within the urinary tract is found to be a more frequent component than is usually appreciated. Our findings do not support the view that hysteria is a common cause of acute urinary retention in females.

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Idiopathic Chronic Urinary Retention in the Female

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Chronic retention of urine in the adult female is an uncommon condition, especially if one excludes patients with obvious extrinsic or intrinsic obstruction and neurological disease. 14 patients with this type of retention were seen over a period of 7 years. The history, course, clinical and laboratory findings, complications and treatment with results are reviewed.

Illustrative Cases

Case 1. Mrs E. W., aged 74 years, gave a 20 years' history of recurrent cystitis. There had been 6 episodes in the past year and for 1 week she was dribbling only. On admission, a non-tender bladder was palpable half-way to the umbilicus. The urine was infected. IVP showed normal upper tracts and a distended bladder (Fig. 1). Cystoscopy confirmed a residual urine of 700 ml; there was minimal trabeculation and a little elevation of the bladder neck posteriorly and postero-laterally. Urethral dilatation to 32 F was performed and a urethral catheter left in place for a 5 days. When removed, the patient continued with a high residual urine and subsequently went into acute retention. A cystometrogram at this stage (Fig. 2) showed a larger capacity than normal and no detrusor responses consistent with an atonic type of bladder. Transurethral resection, taking a loop-full all round the circumference of the bladder neck, was performed. At the end of the procedure fluid was easily expressed from the bladder. After removing the catheter in 1 week, residual urine remained at no more than 50 ml. She was delighted with the result and lost to follow-up after 3 months.

Histological examination of the bladder neck tissue (Fig 3) showed extensive squamous metaplasia and cystitis cystica with several large cysts. Underlying tissue including muscle was essentially normal and there was no significant inflammation apart from isolated aggregates of lymphocytes.

Case 2. Mrs. J. F., aged 60, gave an 8 months' history of poor stream and inadequate emptying feeling of the bladder. Symptoms began while her husband was in hospital with appendicitis. She had previously consulted physicians with symptoms labelled as anxiety dyspepsia and globus hystericus. The bladder was just palpable in the abdomen, urine was sterile and she could not void at the end of the IVP. 150 ml residual urine was found at cystoscopy. There was no trabeculation or obvious bladder neck abnormality. Urethral dilatation to 40 F and

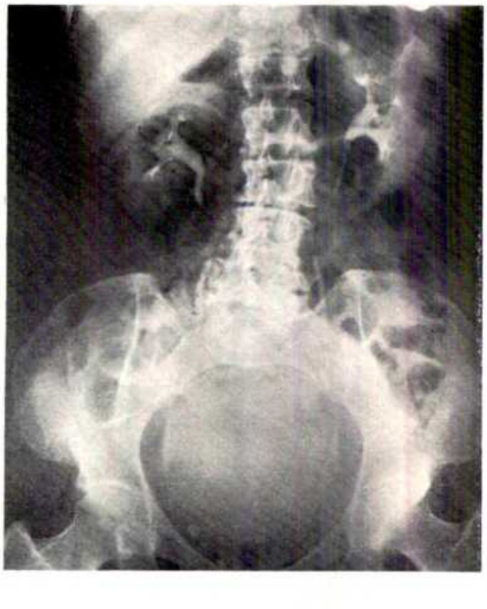

Fig. 1. Mrs E. W. IVP post-micturition film showing distended bladder and normal upper urinary tracts.

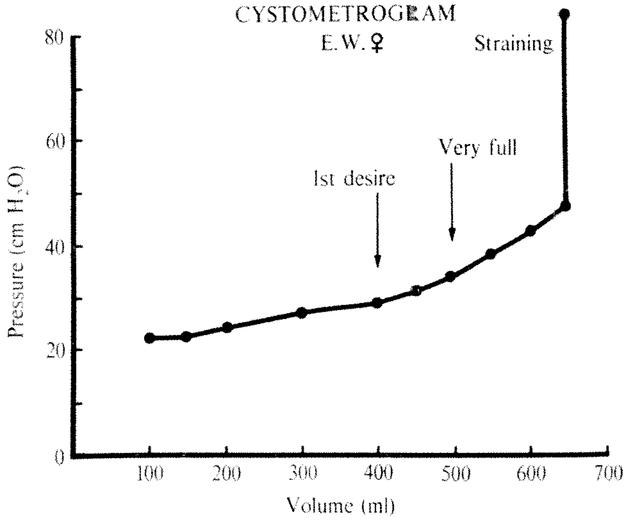

Fig. 2. Mrs E. W. Cystometrogram.

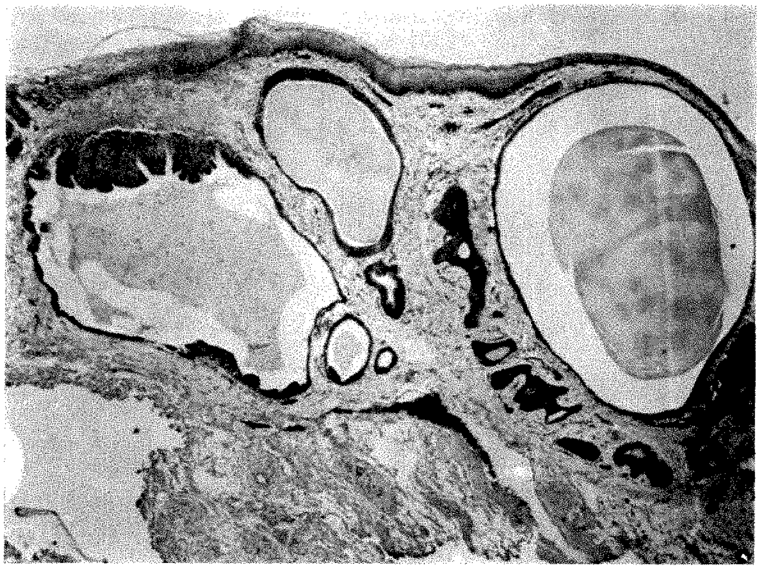

Fig. 3. Mrs E. W. Bladder neck histology. The epithelium shows squamous metaplasia and the underlying tissues show cystitis cystica. H & E. × 30.

subsequent 5 days' catheter drainage produced complete resolution of the symptoms and no residual urine. Follow-up was 2 years.

Case 3. Mrs. A. H., aged 84, gave a 6 months' history of frequency, dysuria and poor stream. The bladder was not palpable; the urine was infected. IVP showed a grossly trabeculated and sacculated bladder (Fig. 4). At cystoscopy 300 ml residual urine was found. The bladder neck was not obviously elevated. Transurethral resection produced an excellent result, only 10 ml residual urine being found 1 year later. Histology (Fig. 5) showed squamous metaplasia of the epithelium and oedema of the lamina propria which contained areas of infiltrate varying from only focal collections of lymphocytes with a more diffuse scattering of inflammatory cells to a focus of more intense inflammation with polymorphs, plasma cells and lymphocytes. The underlying muscle showed some interstitial fibrosis within the muscle fibres (Fig. 6).

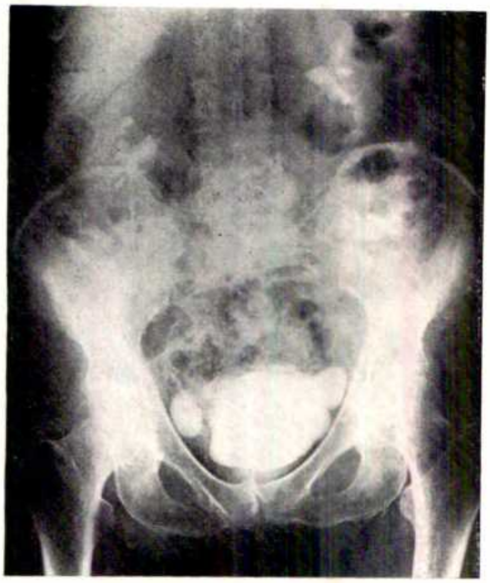

Fig. 4. Mrs A. H. IVP post-micturition film showing sacculated bladder and normal upper urinary tracts.

Clinical Data

The age distribution of the 14 cases was biphasic, 4 were 30 and below, the remainder 50 and above. The youngest was 18, the oldest 84. All patients complained of frequency, 4 had urgency and 2 overflow incontinence. Feeling of incomplete bladder emptying was noted by 6 and a similar number said they had to strain to empty the bladder. Haematuria in 2 and dysuria in 4 were always associated with urinary infection. 4 patients had, in addition, in the recent past had depressive and anxiety symptoms and psychosomatic problems such as globus hystericus.

Duration of urinary symptoms varied widely. It was 2 to 6 months in 4 and 1 year and longer in 10, the longest being 20 years.

Upper urinary tracts were normal in all but 2 of the women. One had vesico-ureteric reflux with dilatation and pyelonephritis; the other a blood urea of 78 mg and congestive cardiac failure. 4 had had previous hysterectomies but in only 1 was onset of symptoms related in time to the operation. Residual urine volumes ranged between 120 and 1500 ml. 10 were in the 120 to 300 ml range and 3 had residual urines of over 900 ml.

Cystoscopy was performed under general anaesthesia and a 22 F instrument passed without difficulty in all but 2 cases. Both of these admitted an 18 F sound but tightness at the external urethral meatus was then found. Cystoscopic findings fell into 2 main groups, those with and those without trabeculation. Trabeculation was present in 7, marked in 2. The others had smooth-walled and rather floppy-type bladders. In 4 the bladder neck appeared raised posteriorly and postero-laterally, a finding not necessarily related to the degree of trabeculation. However, these were the ones who responded to T.U.R. and not to urethral dilatation.

Treatment and Results

Urethral dilatation was the first line of treatment in 11 patients and was performed at the time of the initial cystoscopy. Female straight sounds, then Hagar's dilators up to 12 to 14 size (38 to 44 F) were passed, often with a fair amount of final pressure producing blanching of the external urethral meatus and at times some tearing and bleeding. 4 were cured, 3 improved and 4 remained

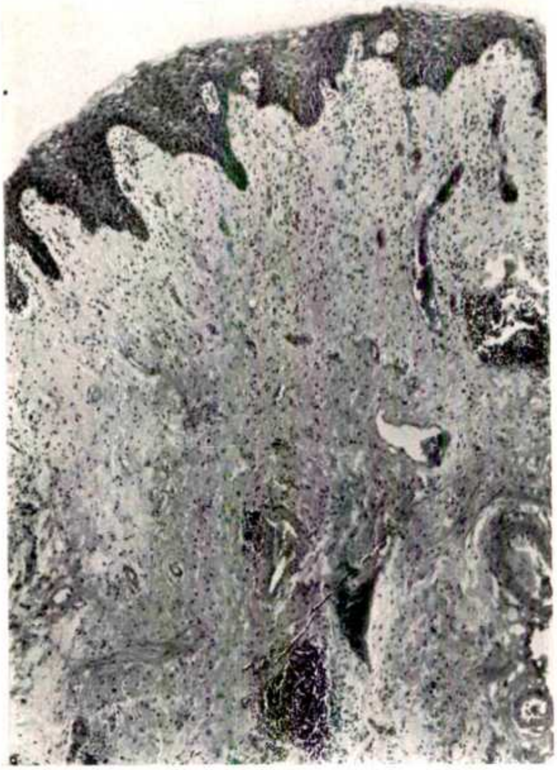

Fig. 5. Mrs A. H. Bladder neck histology. The epithelium shows squamous metaplasia. Diffuse active chronic inflammation with focal aggregates of lymphocytes in lamina propria. H & E. × 60.

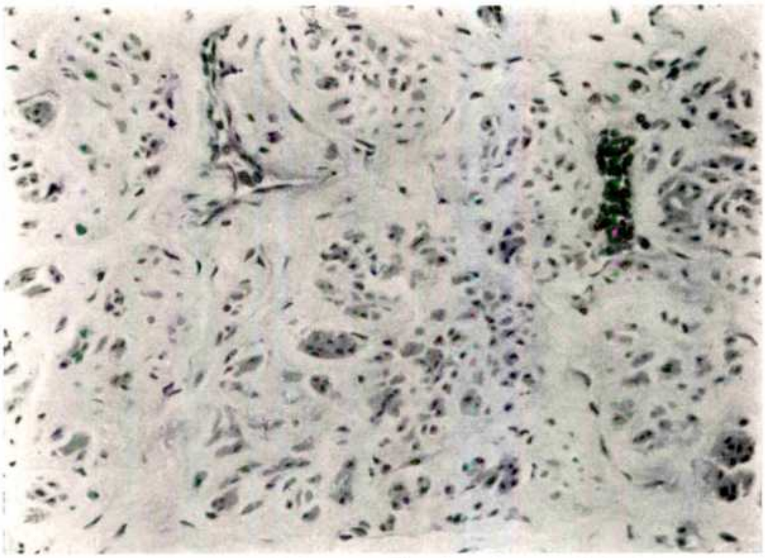

Fig. 6. Mrs A. H. Bladder neck histology. Fibrosis in the muscularis with atrophy of muscle fibres. H & E. × 250.

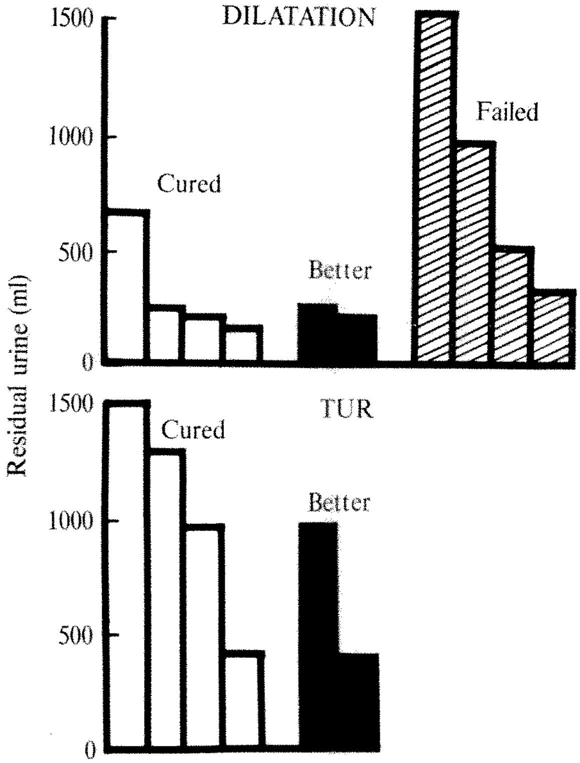

Fig. 7. Idiopathic chronic urinary retention in the female; results of treatment.

the same. The last 4 included the first patient described who was the only one taken to 32 F, and no further. 3 of these were subsequently resected with success; the fourth has not yet been resected. All patients were instructed to practice double micturition for at least 3 months postoperatively and to void no less than 2-hourly in the day. Bethanechol 25 mg 3 times daily was given postoperatively in some of the cases but the effect was uncertain. After *transurethral resection of the bladder neck* in 6 patients, 4 became symptom-free with no appreciable residual urine and 2 were improved. Dilatation improved and cured women with relatively smaller residual urines (Fig. 7) while it failed with the larger ones. T.U.R. was more successful when performed in patients with the largest residual urines and when the bladder neck was noted to be raised.

Histological Findings

Histological specimens were examined in the 6 T.U.R. cases (Table). There was squamous metaplasia of the epithelium in 5 and ulceration in 1. Of those 5 cases 3 showed, in addition, areas of "vaginal" metaplasia such as may be seen in pseudomembranous trigonitis (Henry and Fox, 1971). Cystitis cystica was seen in 4 cases and cystitis glandularis in 2. The lamina propria could be examined in all 6 cases and showed oedema in 2. All of the biopsies showed significant inflammation either in the form of focal lymphocytic aggregates, a diffuse exudate of plasma cells and lymphocytes or areas of more acute inflammation. In some cases the lamina propria showed fibrosis, extending into the superficial muscularis in 5. In 2 instances, fibrosis was seen in relation to the deeper muscle bundles accompanied by atrophy of the muscle fibres.

Discussion

Satisfactory emptying of the bladder depends upon a balance between detrusor activity and resistance of the bladder neck and within the urethra. We now know that obstruction of the neck

Table
Idiopathic Chronic Urinary Retention: Bladder Neck Historical Findings in 6 Patients

	Epithelium				Lamina propria							Muscle		
Patient	Squamous Metaplasia	Vaginal Metaplasia	Cystitis Cystica	Cystitis Glandularis	Oedema	Inflammation	Focal lymphocytes	Diffuse lymphocytes	Plasma cells	Polymorphs	Vascular dilatation	Superficial fibrosis	Deep fibrosis	Atrophy
G. J.	+	+	−	+	−	+	+	+	+	−	+	+	−	−
E. W.	+	+	+	−	−	+	+	−	−	−	−	−	−	−
F. H.	+	−	+	−	−	+	−	+	+	+	+	+	+	+
N. E.	+	−	+	+	−	+	−	+	+	−	−	+	−	−
A. H.	+	+	+	−	+	+	+	+	+	+	+	+	−	−
D. B.	Ulceration				+	+	+	+	+	+	+	+	+	+

of the bladder in women may well be a more common condition than previously thought, as pointed out by Emmett, Hutchins and McDonald (1950), Essenhigh, Ardran and Cope (1968) and Roberts and Smith (1968). It has to be considerably more severe before substantial amounts of residual urine form or complete retention occurs (Glenn and Montgomery, 1964).

The aetiology of this obstruction in the adult female is by no means clear. Evans (1971) observed muscular hyperplasia, inflammatory changes giving rise to oedema, fibrosis and hyperplasia of the epithelium, whilst Roberts and Smith (1968) implicated atrophic post-menopausal changes. Folsom (1931) and Corrin, Mayor and Moore (1963) blamed hyperplasia and inflammation of the urethral glands. Any, or a combination, of the factors may be involved, none of which need be of a marked degree to tip the balance of power between the detrusor muscle and outflow resistance. Findings in this series are no exception. Inflammatory changes and interstitial oedema were noted in all cases from which tissue was examined, prominence of the bladder neck was present in 4 and some narrowing of the urethra in 2. However, only 7 patients exhibited trabeculation, some in the smaller, others in the larger residual urine categories, suggesting that obstruction was not the only cause.

6 patients gave a history of recent marked psychological problems. Only 1 of this group exhibited trabeculation and it was mild. Past ability to hold on to the urine for the whole day was also admitted by 1. A psychogenic element allowing progressively excessive bladder distension may well arise, the so called modesty type of bladder. This group, with a floppy type of bladder, may thus constitute one aetiological category, the other being the obstructive type. When associated with mild bladder neck changes, which may precede or follow as a result of infection, the course is set for a progressive condition.

Response to treatment employed throws further light on the aetiology of this condition as pointed out by Zimskind and Mannes (1973). When the chain of events is broken by dilatation or by transurethral resection, improvement, if not complete resolution, resulted in most cases. We now believe that dilatation should not be below 38 or 40 F size.

When elevation of the bladder neck was noted in association with a large residual urine, that is in the order of 700 ml or above, transurethral resection of the bladder neck was the management of choice. We might have achieved similar results by internal urethrotomy and meatotomy (Bonnin, 1969) but it was felt that T.U.R. removed the elevated inflamed bladder neck tissue, decreased bladder neck resistance more effectively and at the same time provided tissue for histological examination.

Summary

The clinical features in 14 female patients with chronic urinary retention unassociated with extrinsic or obvious intrinsic obstruction or neurological disease are described.

Management, results and histological findings are presented and discussed in relation to the clinical findings.

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Ultrasound Assessment of Residual Urine in Children

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The bladder of a healthy child probably retains no more than a few millilitres of urine after voiding under normal circumstances. Residual urine predisposes to urinary infection, may be evidence of neuropathic bladder dysfunction, and can be a significant factor in producing incontinence and upper urinary tract dilatation. There are many situations in paediatric urology where it is essential to measure residual urine and many other occasions when this information would be useful. A method of assessing residual urine which is simple, accurate, non-invasive and harmless would be of considerable value in clinical practice. None of the currently available methods meets all these requirements; each has its advantages and limitations which are briefly considered:

(1) Clinical Examination. It is routine practice to palpate and percuss for a distended bladder. If a bladder remains palpable after an adequate opportunity to void there is clearly a significant residue. Clinical assessment has obvious limitations: an enlarged bladder may be difficult to appreciate in children who are obese, nervous or unco-operative, or who have abdominal tenderness due to recent surgery or peritonitis, or in children with large floppy bladders such as in the prune belly syndrome.

(2) Catheterisation. This is the most usual method of establishing a residual volume and certainly whenever a catheter has to be passed, for example in performing a cystogram or cystometrogram, the opportunity should be taken to measure residual urine. Repeated catheterisations are undesirable because the procedure causes discomfort, especially in boys, and carries the risk of introducing infection or traumatising the urethra. A catheter usually gives an accurate measurement of residual urine but we have found that with the small size catheters used in children (6 to 10 French gauge) the volume obtained can be misleading.

(3) Radiology. Post-micturition films in the course of intravenous urography and micturating cystography are useful methods of assessing the completeness of bladder emptying, but clearly radiation exposure imposes limitations on their use.

(4) Dye Excretion (Phenol Red) and (5) Radioactive Labelling. (Iodine-131, Technetium-99). Both techniques avoid the use of a catheter and can give accurate quantitative results. Both inquire intravenous or suprapubic injections and have other technical difficulties which make them unsuitable for routine use.

Ultrasound

Ultrasound is now an established diagnostic tool which can make a valuable contribution to the investigation of the urinary tract, particularly in the diagnosis of space-occupying renal lesions. Much of the work in this field has been done in Glasgow, where Professor Donald pioneered the development of ultrasound in obstetrics, and has been the subject of 2 papers to this Association in recent years (Kyle *et al.*, 1971; McLaughlin *et al.*, 1975).

The basic principles of ultrasound have been well described elsewhere (Barnett and Morley, 1972). Briefly, the apparatus consists of a mobile probe containing a transducer which emits short pulses of ultrasonic energy which travel through the tissues. Echoes are reflected back from interfaces and the transducer functions also as a receiver. As the transducer is moved across a selected plane the returning echoes are displayed on an oscilloscope as a series of dots, thus building up a cross-sectional picture. This type of display is referred to as a "brightness-modulated", or B-mode scan. In the A-mode scan ("amplitude modulated") the echo information is displayed as a vertical deflection whose amplitude is related to the intensity of the echo. A

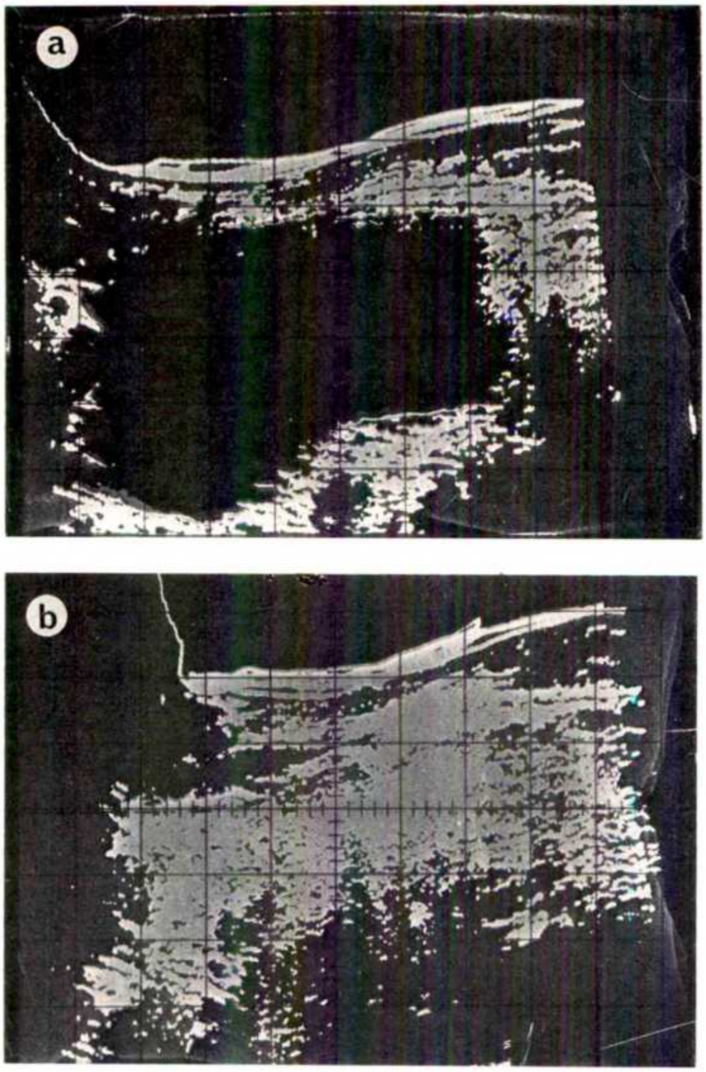

Fig. 1. Midline sagittal scan of a full and empty bladder in a girl, age 10 years, (a) bladder full, (b) bladder empty.

more recent development is the Grey Scale Ultrasound where amplitude is reflected by differing shades of grey.

Ultrasound is particularly good at identifying fluid-filled structures as fluid readily transmits ultrasound, which is reflected from the solid-fluid interface leaving an echo-free space. A full bladder can readily be identified (Fig. 1).

Procedure

The apparatus we have used is a standard commercial unit ("Picker Echoview"), operating at 2·5 MHz, with the information displayed as a B-mode scan.

The child is examined supine with no special preparation. Contact between the transducer and the skin is improved by the use of a coupling agent such as electrode jelly and the probe is moved back and forth across the abdominal wall in the selected plane. The picture can be seen on the

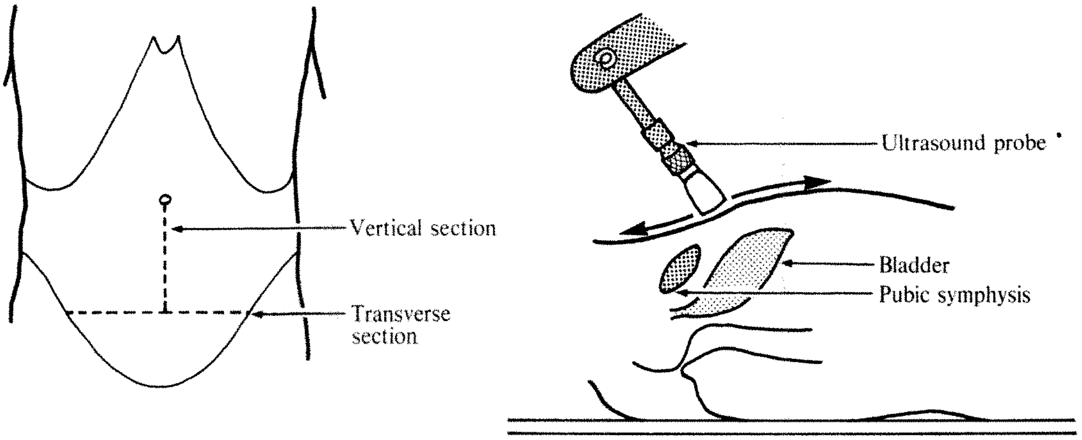

Fig. 2. The technique of bladder ultrasound (see text.)

oscilloscope as it is built up and a permanent record secured by a Polaroid camera attached to the apparatus. We have made measurements both in the vertical (or sagittal) and transverse planes. In the sagittal plane it can be difficult to define the base of the bladder as it lies in the shadow of the symphysis (Fig. 2) but nevertheless we have found this the most useful plane.

Patients

Ultrasound bladder films and residual volumes have been measured in 17 children most of whom have neuropathic bladders. There were 9 boys and 8 girls whose ages ranged from 4 to 15 years.

In 6 children calibration measurements were performed during bladder filling for micturating cystography; a series of ultrasound pictures being obtained at known filling volumes and again after voiding. In other children we have assessed residual by ultrasound at follow-up appointments, establishing the volume by catheterisation whenever possible.

Findings

(1) A filled bladder and an empty bladder could be readily appreciated by ultrasound (Fig. 1).

(2) With incremental filling of the bladder, changes in bladder size could be appreciated in sagittal sections but much less change was generally apparent in the transverse plane (Fig. 3). In the transverse plane there was also the difficulty of defining the level of section and for these reasons we decided to concentrate on the sagittal plane with the midline as a ready reference point. Even then the information obtained could be misleading if the bladder enlarges asymmetrically (Figs. 4 and 5).

(3) To test the correlation between the ultrasound picture and bladder volume we measured bladder size in 2 planes at right angles directly from the photographs and plotted the product against volume. The results show a good straight line relationship for individual patients and for the mean values overall (correlation coefficient 0·99) (Fig. 6). However, the standard errors and standard deviations have a wide scatter which means it is not feasible to make an accurate quantitative calculation of residual volume from a single ultrasound reading.

Discussion

Estimating the volume of an organ of variable shape from a single-plane picture is fraught with difficulties. The area of the bladder shadow seen in post-micturition radiographs is known to

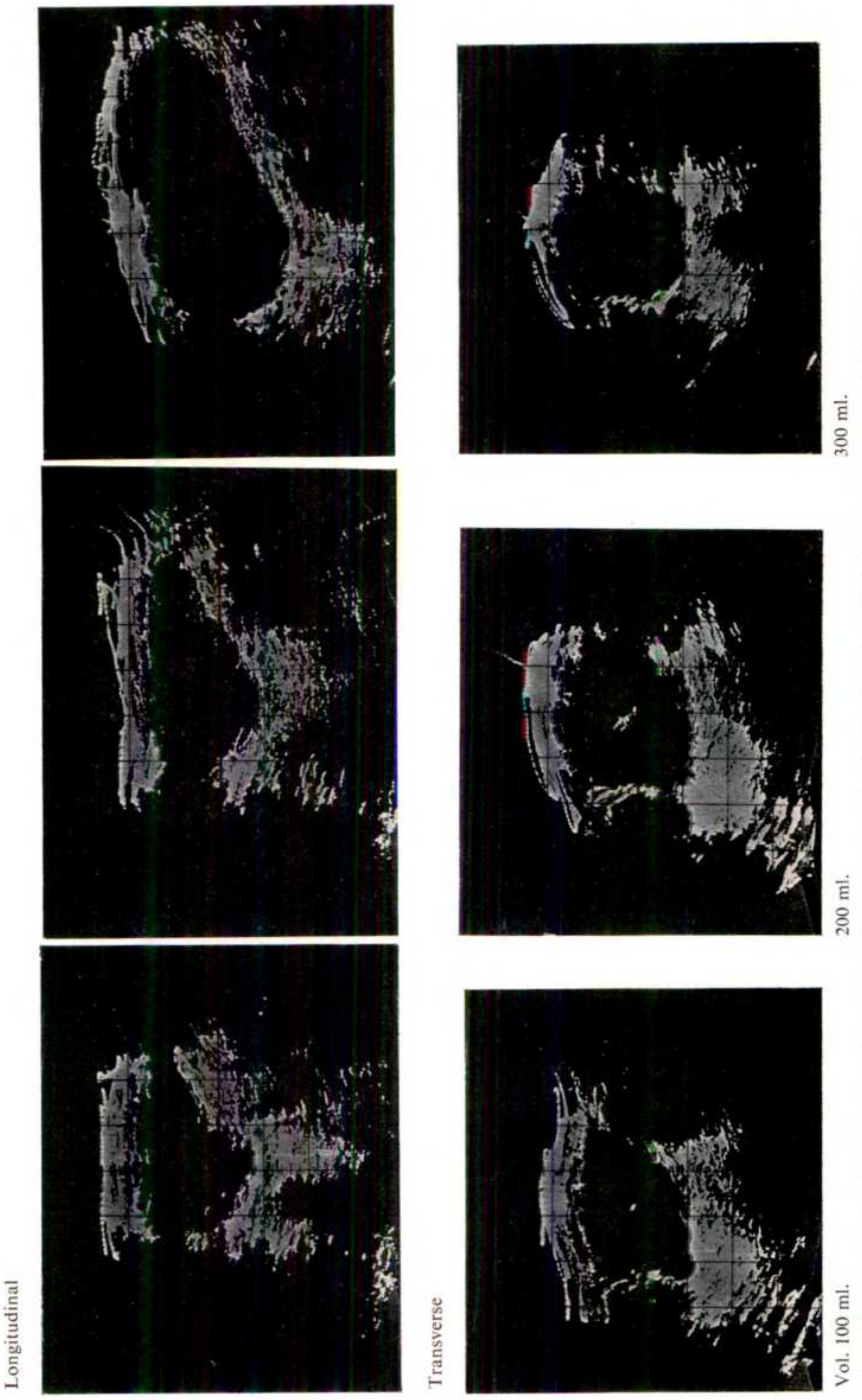

Fig. 3. Incremental bladder filling showing increase in bladder size on longitudinal scan but little change on transverse (girl, age 6 years).

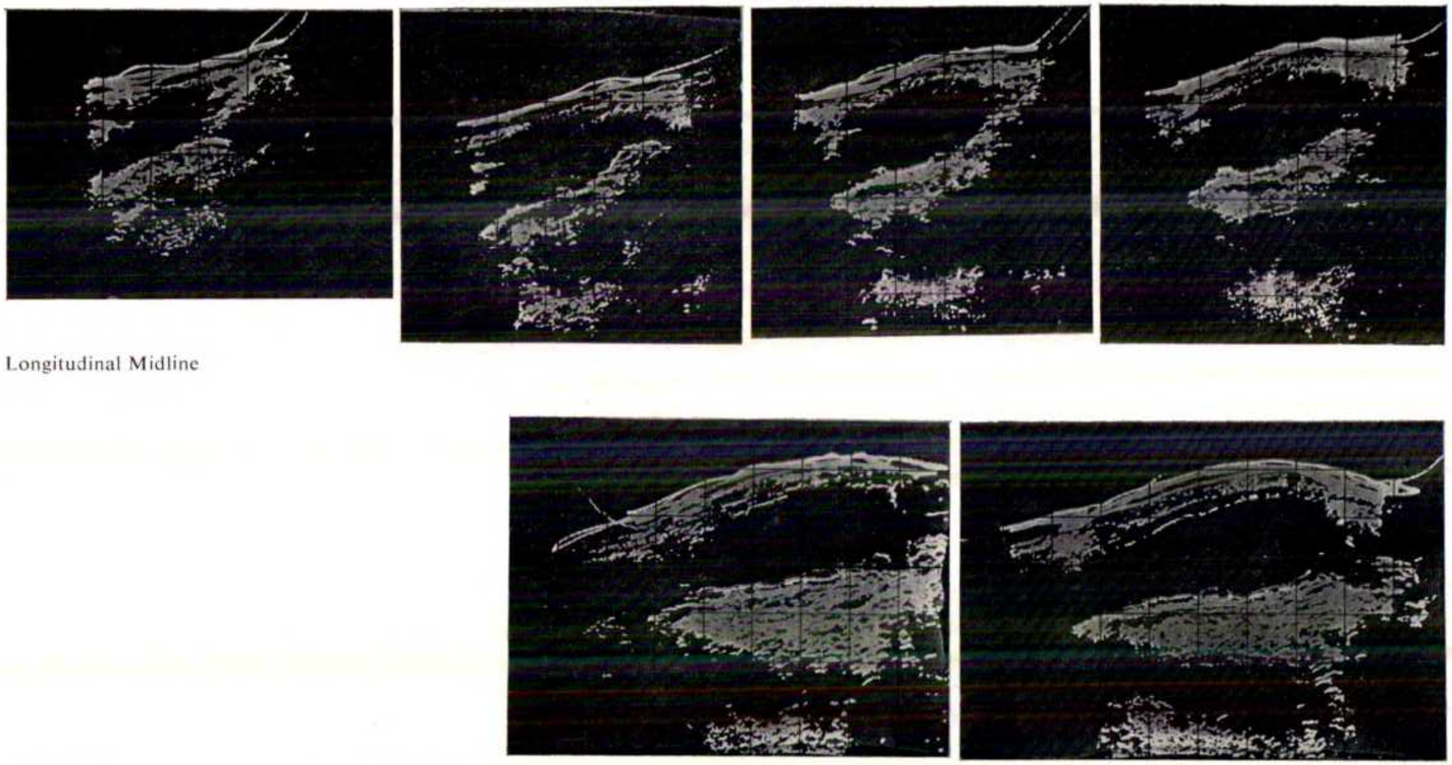

Fig. 4. Incremental bladder filling showing increase in bladder size only when probe positioned to right of midline (boy, age 6 years, with neuropathic bladder).

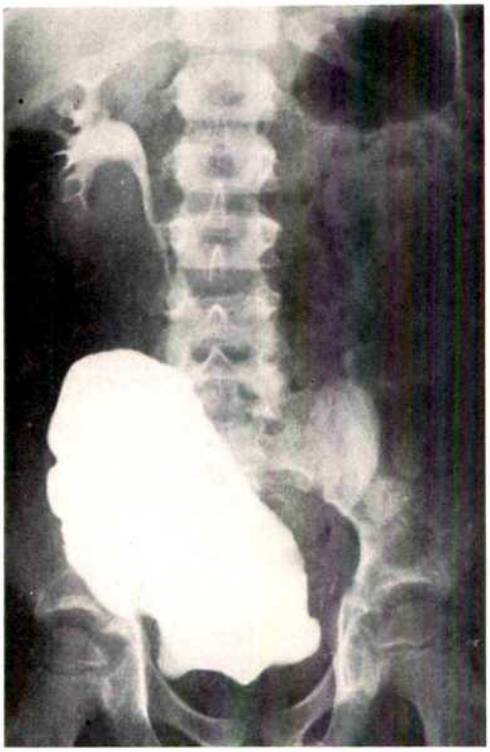

Fig. 5. Intravenous urogram in same patient as Fig. 4 showing asymmetrical bladder enlargement.

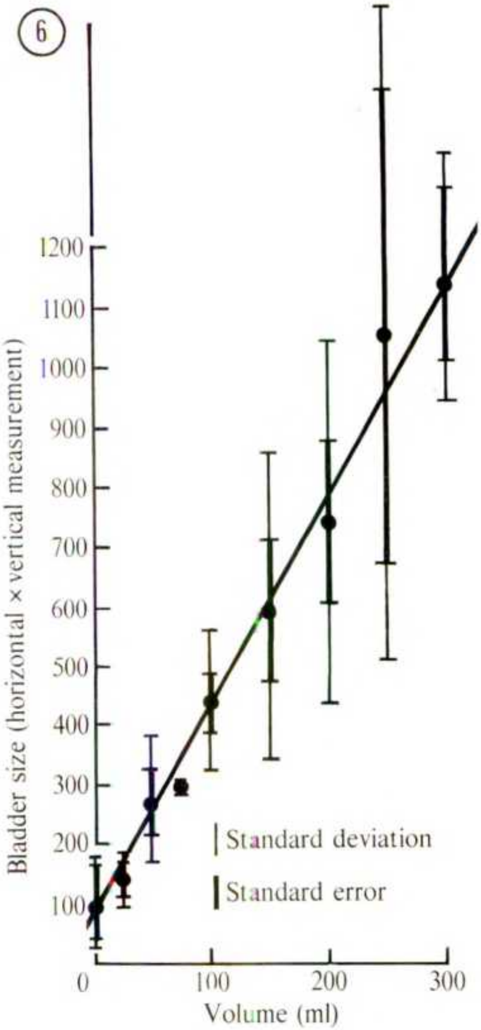

Fig. 6. Bladder size measured from ultrasound pictures plotted against bladder volume. Correlation coefficient on means = 0·99.

correlate poorly with residual volume, showing an error of up to 50% (Bretland, 1958). Extrapolating residual volume from ultrasound picture is likely to be subject to similar difficulties. Indeed, this has been the experience reported by others who have used ultrasound to assess residual urine in adults, even when more complex mathematical analysis was applied (Holmes, 1967; Alfthan and Mattsson, 1969). However, this does not mean that ultrasound is of no value in assessing residual urine but rather that it is important to appreciate its limitations. In many clinical situations a semi-quantitative assessment is sufficient. For example, we have used the technique in children with neuropathic bladder disorders to follow the response to treatment with alpha-adrenergic blocking drugs (Figs. 7 and 8). In this kind of situation when repeated examinations are required the advantages of ultrasound are considerable. The procedure is simple, non-invasive, takes only a few minutes to perform and requires minimal patient co-operation. Children may show some initial apprehension but it is readily overcome and they will happily undergo repeated examinations on subsequent visits. This is in marked contrast to

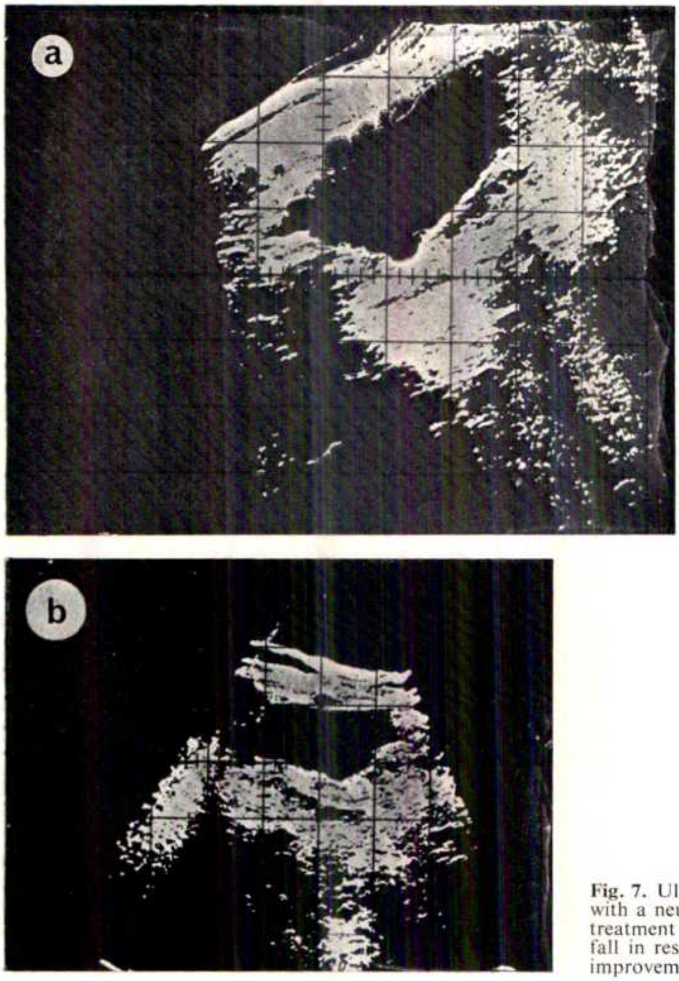

Fig. 7. Ultrasound residuals in a girl, age 4 years, with a neuropathic bladder (a) before and (b) after treatment with phenoxybenzamine. There has been a fall in residual volume together with symptomatic improvement.

the distress which catheterisation causes to nearly all children. As no special preparation is necessary for ultrasound examination the technique is very suitable for out-patients.

Often, all that is required of the investigation is to establish the presence or absence of residual urine and this ultrasound can do with certainty (Fig. 9). Taking measurements from the ultrasound pictures will rarely be necessary as with practice the eye can judge changes in area quite well. If quantitative values are required it would be better to construct a calibration graph for that particular patient at an initial examination, such as at the time of a cystogram, as described earlier. For more accurate quantitative measurement of residual urine a catheter remains the method of choice. Alternatively if catheterisation is contra-indicated a radioactive labelling technique can give extremely accurate measurements of residual volume.

At one time there was concern that ultrasound might carry a risk of causing cell damage or chromosomal changes, as had been shown in animal experiments but there is no evidence that this occurs at diagnostic intensities and ultrasound has been safely used in obstetrics for 13 years (Donald, 1962).

Ultrasound equipment is expensive and no one would suggest acquiring the apparatus solely for assessing residual urine. However, if an ultrasound machine is already available—and its

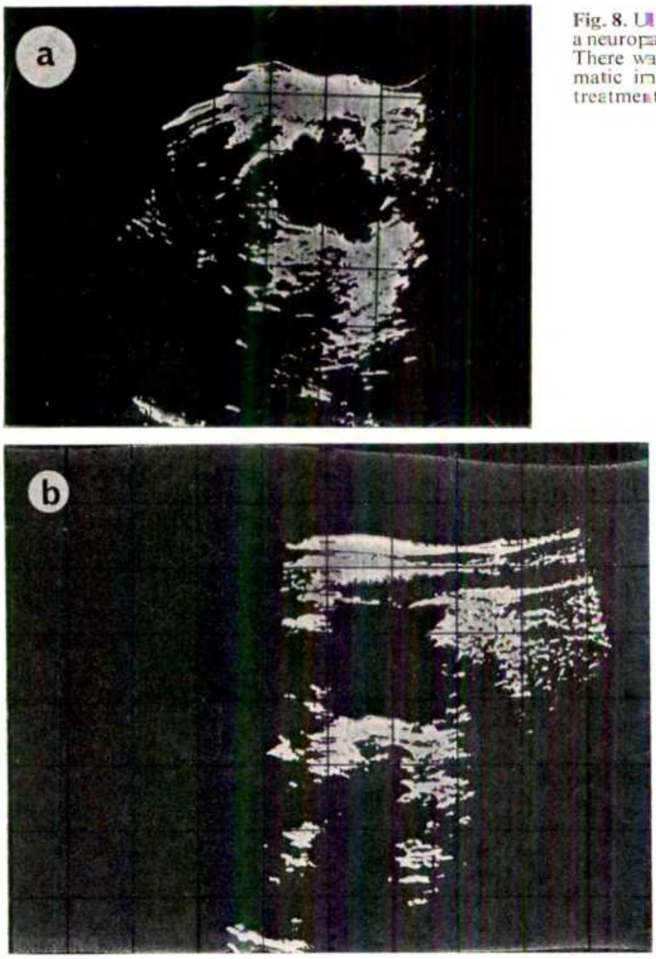

Fig. 8. Ultrasound residuals in a boy, age 6 years, with a neuropathic bladder treated with phenoxybenzamine. There was no reduction in residual and no symptomatic improvement (a) before treatment, (b) after treatment.

value in obstetrics and in the diagnosis of renal masses is sufficiently established to justify its provision in District Hospitals—then here is a further use for which it can be recommended.

Conclusions

1. Ultrasound can be used for assessing residual urine semi-quantitatively.
2. Midline sagittal scans are recommended.
3. Ultrasound has the following advantages:
   - (i) It is simple, quick and requires no preparation.
   - (ii) It is non-invasive and free from harm.
   - (iii) It can be performed repeatedly, and is acceptable to children.

Summary

Ultrasound has been used to assess residual urine in children and found to have considerable advantages over other methods. Using a B-mode scan in the sagittal plane the presence or absence

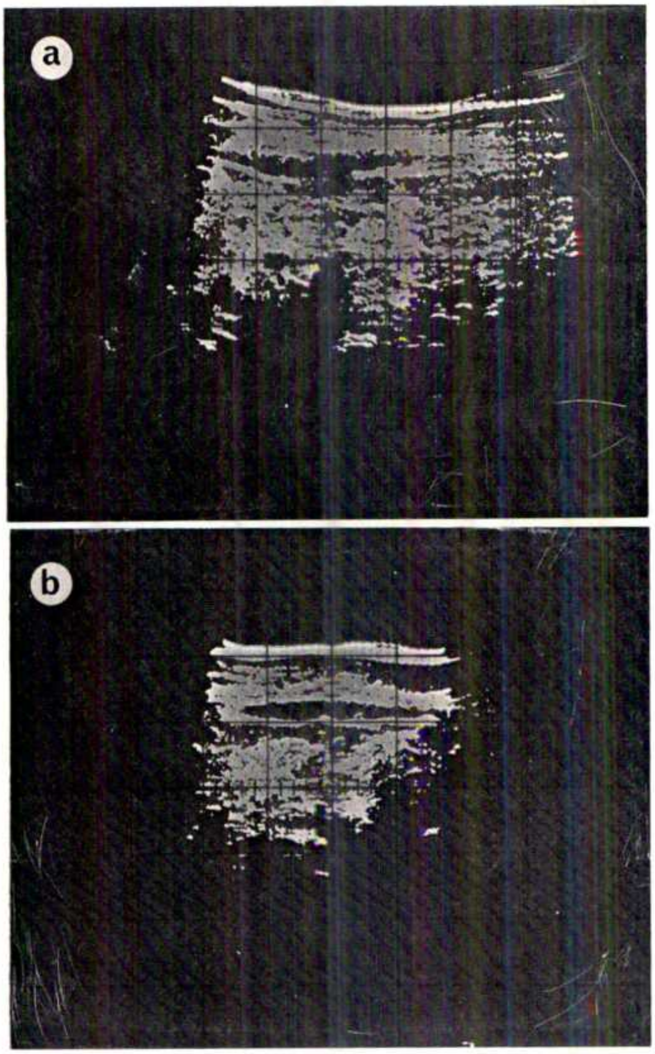

Fig. 9. Ultrasound appearance of a bladder with no residual urine (girl, age 10 years) (a) Longitudinal, (b) Transverse.

of residual urine can be confidently determined. Quantitative measurements of volume are subject to considerable error but semi-quantitative information in individual cases can be obtained by comparison of records made at subsequent examinations. More accurate quantitative values might be achieved by constructing an individual calibration curve.

The advantages of ultrasound for assessing residual urine are that it is simple, quick, harmless and non-invasive. Because of these features the examination can be readily repeated, is suitable for out-patient use and is acceptable to children.

We are grateful to Mr D. Innes Williams for allowing us to study children under his care and for his advice and encouragement.

Dr D. Werry carried out some of the ultrasound examinations, and the illustrations were prepared by the Department of Medical Art and Photography at the Institute of Urology.

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A Urodynamic View of Bladder Outflow Obstruction in the Female: Factors influencing the Results of Treatment

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In many ways both the diagnosis and the treatment of bladder outflow obstruction are more complicated in the female than in the male. We have reviewed our findings in 2,500 females referred to our Urodynamic Clinic at the Middlesex Hospital and, just as in the male (Turner Warwick *et al.*, 1973), some commonly held precepts relating to the diagnosis of outlet obstruction in the female must be questioned.

Only 169 patients fulfilled the criteria of outlet obstruction that have been adopted for the purposes of this communication and it proved impossible to identify these on the basis of a symptom analysis alone; micturition symptoms relevant to the voiding stream are only exceptionally diagnostic; and although urinary infection commonly occurs in such bladders it is much commoner still in bladders that are dynamically normal.

Attempts to identify a urodynamic abnormality of urethral function by bougie-à-boule calibration are essentially erroneous in concept; this indicates only the limit of passive urethral wall stretching. In order to produce a significant degree of obstruction the calibre of a rigid stricture has to be quite small, in the region of 10 to 12 F; a rigid stenosis of this size is a rare occurrence in the female.

A so-called "meatal stenosis" calibrating to 20 F is by no means indicative of obstruction; any associated outflow obstruction must be the result of a dyssynergic failure of the urethra to attain its potential calibre during voiding whether this is due to muscular activity, tissue elasticity or distortional factors: *per contra*, a urethra which calibrates in excess of 30 F may be associated with severe urodynamic outflow obstruction.

The endoscopic evaluation of urethral obstruction is notoriously inaccurate in the female. Although obstruction at the bladder neck level in the female is often diagnosed (and treated) it is in fact most unusual, except when an a-contractile (atonic) bladder fails to open at the bladder neck (Turner Warwick *et al.*, 1973). The endoscopic appearances of trabeculation are not indicative of outflow obstruction in the female. Simple transillumination of such a bladder wall often shows it to be translucent except for coalescent bands of residual muscle fibres and these bladders commonly evacuate at low pressures and are stable. Detrusor hypertrophy also creates the appearance of trabeculation but hypertrophy is an unusual response to the degree of bladder outflow obstruction that commonly occurs in the female; it is more often associated with an unstable detrusor mechanism and possibly a consequence of uninhibited detrusor activity against a closed sphincter mechanism.

Attempts to identify, locate, or assess a degree of outflow obstruction by urethral pressure-profile measurements are disappointing since the static pressure state bears little relationship to urethral dynamics during voiding.

While simple voiding cysto-urethrography is of fundamental diagnostic value in the location of a proven outflow obstruction in the absence of synchronous pressure and flow measurements it is of limited value in its identification. The so-called "spinning-top" urethra is certainly not diagnostic and a visual estimate of the flow rate during simple micturating urethrography is commonly inaccurate.

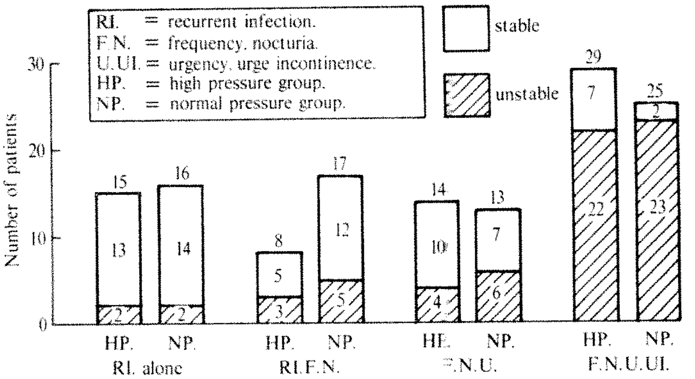


Fig. 1. Presenting symptoms of patients with outlet obstruction related to the dynamic state of the detrusor.

A large post-voiding residual urine is obvious evidence of voiding inefficiency; when it occurs in the absence of an endoscopically detectable obstruction it is commonly assumed to be the result of an "atonic" bladder though, in reality, subtracted detrusor pressure studies may prove the detrusor to be normal and the urethra to be dynamically obstructive. The absence of a residual urine does not exclude a significant outlet obstruction (Turner Warwick *et al.*, 1973).

Vesico-urethro-vaginal prolapse is as irrelevant to the diagnosis of bladder outflow obstruction as it is to the presence or absence of stress incontinence; it may, however, be associated with a significant obstructive element as a result of urethral distortion (Turner Warwick and Whiteside, 1969) but this is particularly difficult to evaluate objectively. Urethral distortion rarely causes obstruction but it can be very troublesome when voiding is supplemented or substituted by abdominal straining because the resulting intra-abdominal pressure is disproportionately distributed around the female urethra; hence the problems of restoring voiding balance to a true atonic bladder in the female.

While a high-pressure/low-flow state is readily acceptable as dynamic evidence of outflow tract obstruction (even in the absence of an anatomically defined abnormality), just as real in dynamic terms is the concept of a normal or low-voiding pressure in association with a low-flow state constituting a relative outflow obstruction. Voiding efficiency is essentially a matter of balance between voiding forces on the one hand and an outflow resistance on the other; a disturbance of either may result in outflow obstruction.

A significant degree of bladder outflow obstruction certainly occurs in the female but it is relatively uncommon and severe obstruction is exceedingly rare. Since the clinical identification of outflow obstruction is beset with so many difficulties it is important to identify a group of patients for study; we have used the peak voiding flow rate as an objective screening test and confined our attention to those patients with detrusor muscle activity whose voiding flow rate is less than 15 ml per sec when seated in private and voiding a measured volume of more than 200 ml. This criteria of outflow obstruction cannot be regarded as absolute for occasional patients void with a higher peak flow created by a greatly elevated detrusor pressure and may be significantly obstructed, whereas others, with a low or even intermittent flow, a rebalanced cystoplasty for instance (Turner Warwick, 1970*a*), may not be significantly obstructed overall and treatment aimed at gaining urodynamic perfection might be ill advised.

Clinical Material

We have identified 169 patients with outlet obstruction and have analysed the results of treatment of the obstruction. Patients with true atonic (acontractile) bladders and the cystoplasty group were excluded as both these constitute separate problems; patients with overt or suspected neuropathy and diabetes were also excluded.

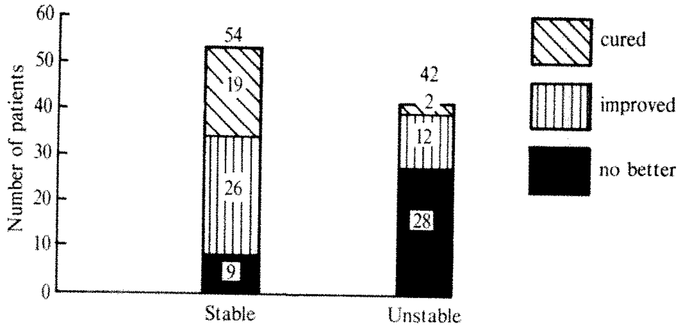


Fig. 2. Results of treatment in patients with stable and unstable bladders.

The 169 patients studied had an age range of 6 to 80 years (mean 47). The technique of micturating video cystography with synchronous flow and subtracted pressure studies has been well documented (Bates, Whiteside and Turner Warwick, 1970; Bates, 1971; Bates and Corney, 1971; Arnold, 1974). All the patients had a free voiding flow rate of less than 15 ml per sec; on the basis of subtracted detrusor pressure studies they were divided into an elevated pressure group with a pressure in excess of 50 cm water (84) and a normal pressure group with a voiding detrusor pressure of less than 50 cm water (85). Only 10 patients in the elevated pressure group had high pressure detrusor levels in excess of 100 cm water.

In 165 of the 169 patients the site of the obstruction was radiologically proven to lie within the distal urethra; in only 4 cases, which were all in the elevated pressure group, the site of the obstruction was at the bladder neck—confirming that it is a rare site in females.

Most of the patients presented either with symptoms of recurrent urinary tract infection (with or without other micturition symptoms such as frequency and nocturia between bouts of infection) or with frequency, nocturia and urgency (with or without urge incontinence). Although some patients admitted to having a poor stream or a sense of incomplete evacuation, only a minority of patients complained of difficulty in micturition. Some patients had associated stress incontinence although only in 5 patients was it the main presenting symptom. The main presenting symptoms have been divided into 4 groups and analysed specifically to define the relationship between these symptoms and detrusor instability (Fig. 1). The presenting symptoms of 32 patients did not fit into the 4 main symptom groups. The overall incidence of detrusor instability was 46% in the elevated pressure group and 47% in the normal pressure group. In view of the obvious similarity in the elevated and the lower pressure groups, both in the incidence of detrusor instability and the presenting symptoms, we have felt justified in considering the 2 groups together for the remainder of this paper.

Treatment

The purpose of this paper is to consider the effect on symptoms of correcting urodynamically proven outflow obstruction.

Bladder Neck

A clinical presumption that bladder outlet obstruction in the female is the result of a bladder neck abnormality would be likely to be more than 95% inaccurate. Erroneous ablation of the bladder neck is a potential disaster for the normal bladder neck is a cough-competent strain-proof mechanism upon which most females depend for continence, particularly stress-continence, because the distal urethral mechanism of the female is relatively inefficient compared with that of the male (Turner Warwick, 1970*b*).

When a urodynamically proven outflow obstruction is radiologically proven to be located at the bladder neck it can be accurately and selectively relaxed by direct incision using a fine knife-blade and a nasal or posterior urethral retractor; this is both efficient and sufficient. We

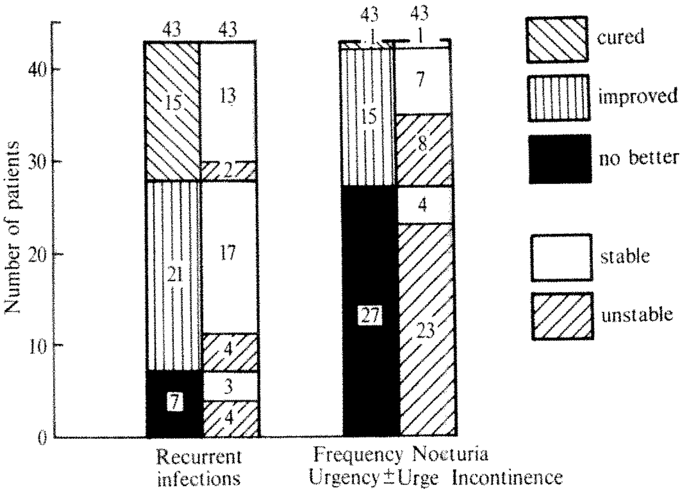


Fig. 3. Results of treatment related to the main presenting symptoms and the dynamic state of the detrusor.

prefer an anterior incision in the 12 o'clock position since this offers the best chance of subsequent retropubic repair if incontinence should result (Turner Warwick *et al.*, 1973).

Unless the bladder neck is obstructed because of extensive secondary scarring it is not necessary to use a Y-V plasty to produce relaxation; indeed such a procedure commonly ablates a considerable length of the intrinsic urethral sphincter.

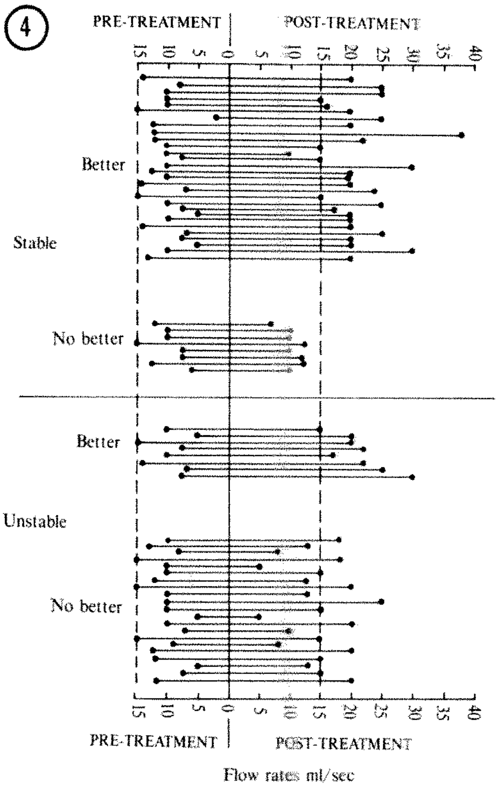
The Intrinsic Urethral Mechanism

The surgical relaxation of the female urethra presents no mechanical problem; recalibration by an expanding instrument such as the Otis (which is essential for the same procedure in the male), with or without the knife incision, may be convenient but is not essential for there is free access both for over-dilatation to an unlimited calibre and for direct internal urethrotomy with a speculum.

It is not the purpose of this paper to compare the results of different procedures for urethral adjustment, especially as the method of Otis instrumentation must be carefully specified for it can be used in a variety of ways. We ourselves only use the knife blade to start a recalibration if there is resistance, the subsequent extent of the recalibration being achieved by simple expansion so that the result is probably not much different from simple over-dilatation.

In general it seems that:

1. Simple office dilatation rarely improves the urodynamic findings.
2. Over-dilatation under anaesthesia to a calibre of 40 to 45 F, whether by dilatation or Otis expansion, commonly, but not always, relieves a proven distal urethral obstruction at least for a time, and such a degree of recalibration carries little risk of impaired urinary control.
3. Gross over-dilatation to finger size (60 to 70 F and above) is occasionally necessary to overcome a relative outflow obstruction in the female but this should always be done in cautious stages with interval readjustment; recalibration in excess of 45 F should probably



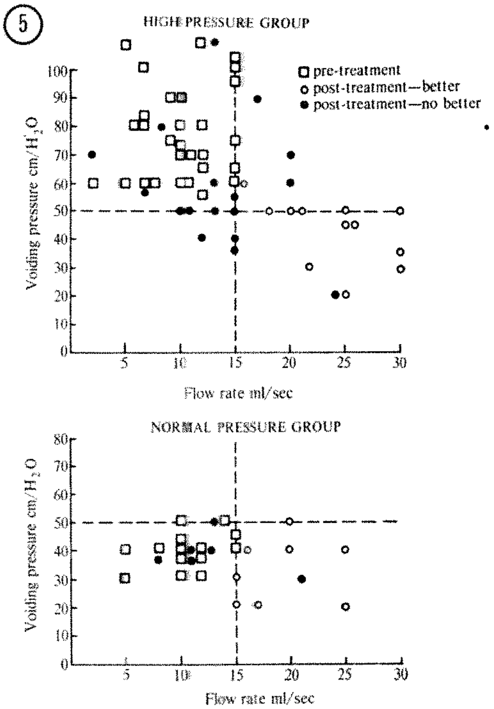


Fig. 4. Pre- and post-treatment peak flow rates in patients with stable and unstable bladders.

Fig. 5. Pre- and post-treatment voiding pressures and flow rates.

never be undertaken until the possibility of a distortional element (Turner Warwick and Whiteside, 1969) has been carefully considered, and treated if necessary, lest it compromise unnecessarily the sphincteric competence of the residual urethral mechanism.

Results

The bladder outflow obstruction of 102 out of 169 patients in this series has been treated and the results analysed. 39 of the remaining patients were referred from other units specifically for diagnosis, a further 9 have been lost to follow-up or defaulted and the treatment of the remainder has been deferred for a variety of clinical reasons. 6 of the 102 patients treated subsequently defaulted from follow-up.

The results of treatment have been related to the state of detrusor stability (Fig. 2). Patients were classed as symptomatically cured only if they had no micturition symptoms after treatment. The symptoms of 45 out of 54 patients (83%) with stable detrusors were either cured or improved by effective relief of their outflow obstruction as opposed to only 14 out of 42 patients (33%) in the unstable group; only 2 patients (5%) in the latter group were cured of their symptoms compared with 19 patients (35%) in the stable group.

The results of treatment have been further analysed, relating them to the main presenting symptoms (Fig. 3). The patients who presented with recurrent urinary tract infection, either alone or combined with other symptoms, benefited most from treatment; the majority of these patients had stable detrusors. Conversely, patients with persistent frequency and nocturia associated with urgency, and often urge incontinence, showed results of treatment which were disappointing; the majority of these patients had underlying detrusor instability.

Pre- and post-treatment peak flow rates were compared in 66 patients (Fig. 4) and related to the results of treatment. Improvement of symptoms correlates well with relief of obstruction (*i.e.* a flow rate in excess of 20 ml per second) in patients with both stable and unstable detrusors. The failures in the stable group are still obstructed but in the unstable group, even though there may have been relief of the obstruction, there has been no symptomatic improvement, the persistent symptoms being due to the underlying detrusor instability; others in this group are still obviously obstructed.

There were no conversions from instability to stability (or vice versa) following relief of the obstruction. An analysis of the voiding detrusor pressures and peak flows of 44 patients studied by video-cystography before and after treatment is shown in Fig. 5. Improvement of symptoms was associated with relief of obstruction.

15 patients had residual urine in excess of 200 ml prior to treatment. 9 of the patients were in the elevated pressure group and the residual urine was associated with premature decompensation of the detrusor during voiding, the remaining 6 patients were in the low pressure group and had poor detrusor activity though they were not atonic. All these patients had more than 1 relaxation of their outlet but even then the results of treatment were disappointing. There was symptomatic relief in 6 out of the 10 patients with stable detrusors but none in the 5 with unstable detrusors.

Discussion

The symptomatic improvement obtained from empirical treatment of bladder outflow obstruction in reported series is only moderately satisfactory in that about one-quarter of patients do not benefit from the treatment (Davis 1956; Kerr, Leadbetter and Donahue 1966; Roberts and Smith 1968; McLean and Emmett 1969; Keitzer and Allen 1970; Immergut and Gilbert 1973; Farrar, Green and Ashken, 1973). These failures have to be explained. In our series of patients in which the outlet obstruction has been identified objectively it is clear that when patients failed to obtain symptomatic relief following urethral dilatation, it was either due to inadequate treatment which did not relieve the outlet obstruction or to the underlying detrusor instability which was responsible for the persistence of symptoms following the relief of obstruction. It seems likely that these two factors probably account for the majority of failures in other reported series.

In patients with stable detrusors the results of pressure and flow measurement show that relief of obstruction correlates with an improvement in the symptoms and conversely that an inadequate relief of obstruction is associated with persistence of symptoms. 83% obtained symptomatic relief and this correlated with an improvement in their flow rate. The 17% of failures of initial treatment in this group proved to have persisting obstruction.

On the other hand, patients with unstable detrusors did not necessarily benefit symptomatically even if the obstruction was relieved; in such cases symptoms would appear to be due mainly to the detrusor instability rather than the outlet obstruction and the overall symptomatic relief obtained in such patients was only 33%.

We have not found any evidence of reversible instability in this series following the relief of outflow obstruction; in this way the detrusor response to outlet obstruction appears to differ from that in the male where conversion commonly follows relief of the obstruction (Turner Warwick *et al.*, 1973) but there is also a difference in the degree of obstruction and the detrusor response in general is different.

Patients whose main presenting symptoms were those of recurrent urinary tract infection benefited most from relaxation of the outlet, irrespective of the state of the detrusor, although those in the unstable group were often left with an abnormal micturition pattern resulting from the underlying and probably incidental detrusor instability.

There are numerous reported series in the literature recording the results of dilating the female urethra by a wide variety of procedures and there is considerable discussion as to what constitutes an adequate recalibration. Obviously it cannot be deduced merely from the description of the procedure nor from the precise measurement of the recalibration since many factors are concerned and naturally both the subjective and the objective functional results of a simple mechanical process are extremely variable.

We have therefore attempted to correlate the urodynamically evaluated indications and results with symptomatic improvement but this is only one aspect of the problem. Office dilatation for instance may appear to be symptomatically helpful to some patients but the reason for this is not clear, for the minimal degree of this recalibration does not usually result in a detectable urodynamic improvement; on the other hand the tendency of some patients to develop a urinary infection may be reduced by converting an acceptably normal voiding efficiency to a supernormal efficiency.

It is clear that comparison of the different forms of treatment for outlet obstruction cannot be reliably based upon symptomatology nor upon simple clinical assessments; adequate pre- and postoperative urodynamic evaluation is essential if such a comparison is to be meaningful and the dynamic state of detrusor stability must also be known.

Summary

169 female patients with outlet obstruction have been studied urodynamically.

The results of treatment of the outlet obstruction in 102 patients have been analysed and the reason for the failures discussed. Patients with stable detrusors and those with symptoms of recurrent urinary tract infection responded well to treatment, provided this relieved the obstruction adequately; symptomatic relief was less common in patients with unstable detrusors, despite adequate outflow readjustment.

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The Effect of Adrenergic Blocking Drugs on Outflow Resistance

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The importance of the parasympathetic nervous system in micturition is not disputed but the role of the sympathetic nervous system is the subject of much debate. The close anatomical relationship between the 2 systems is now recognised (El-Badawi and Schenk, 1966) and Sundin (1972) has shown that the sympathetic system may assume greater importance in the parasympathetically denervated bladder.

The components of outflow resistance may be considered as including the bladder neck, the external sphincter and the so-called intrinsic urethral mechanism (Turner Warwick *et al.*, 1973) to which smooth muscle and elastic fibres in the urethral wall, the mucosal folds and the submucosal plexuses all contribute. Experimental work in animals (Raz, Zeigler and Caine, 1973) has shown that alpha adrenergic stimulation causes an increase in outflow resistance as measured by the urethral pressure profile while alpha blockade causes a fall in outflow resistance. Beta stimulation and blockade have a reciprocal effect.

The present study was designed to assess the effects of alpha and beta adrenergic blocking drugs on the urethral pressure profile in man and to determine whether, at a dose producing minimal cardiovascular effects, significant alterations in outflow resistance could be produced.

Patients and Methods

The 35 patients studied were all fit, with ages ranging from 19 to 71. Patients with a history of ischaemic heart disease or currently taking any medication were excluded. Pulse rate, blood pressure and electrocardiogram were monitored before and after the administration of either phentolamine in a dose of 0·1 mg/kg intravenously or propranolol in a dose of 0·02 mg/kg intravenously. The urethral pressure profile was recorded with the patient supine by the method described by Brown and Wickham (1969) as modified by Harrison and Constable (1970).

Table I

Alpha Block Group

Diagnoses	No. of patients
Idiopathic instability	9
Sphincter weakness	6
Chronic retention	4
Neuropathic bladder	2
Mixed sphincter weakness and instability	2
Benign prostatic hyperplasia	1
Bladder neck obstruction	1

Table II

Beta Block Group

Diagnoses	No. of patients
Idiopathic instability	7
Chronic retention	1
Sphincter weakness	1
Bladder neck obstruction	1

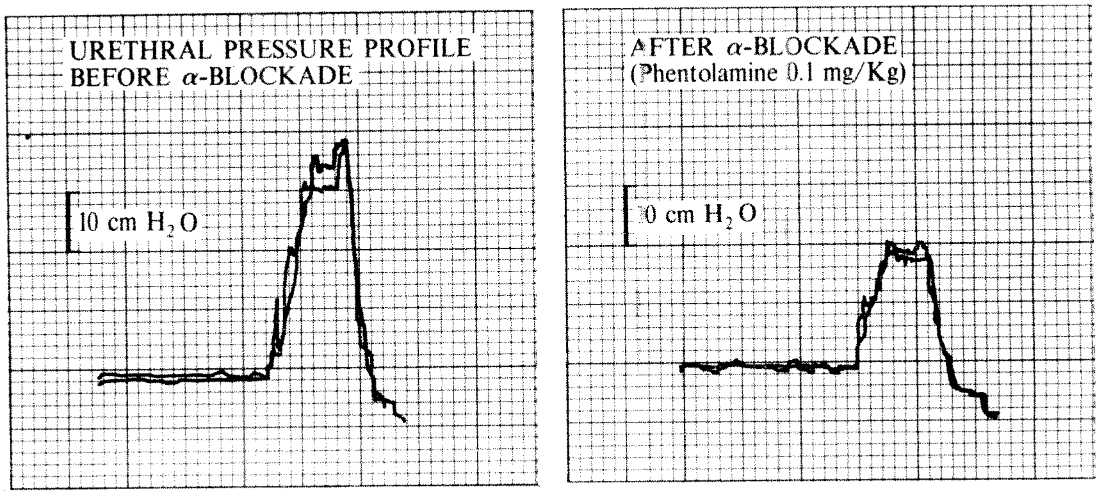
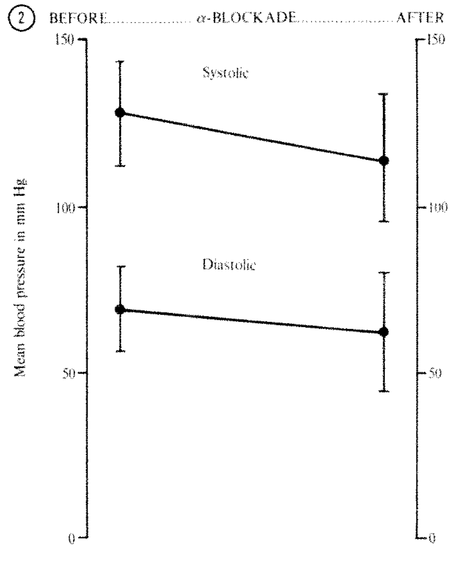


Fig. 1. Urethral pressure profile before and after alpha adrenergic blockade.



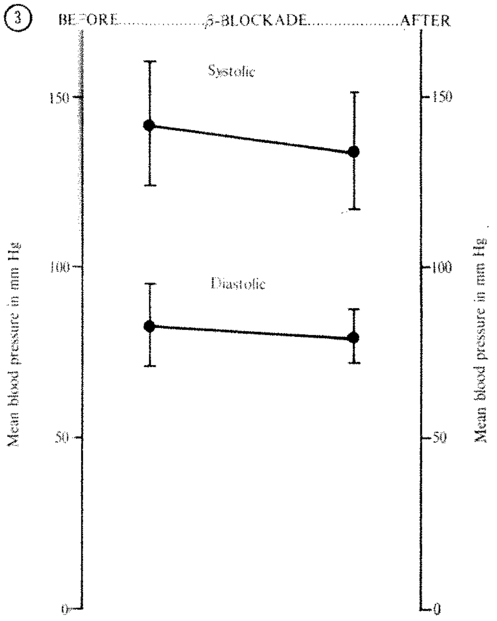
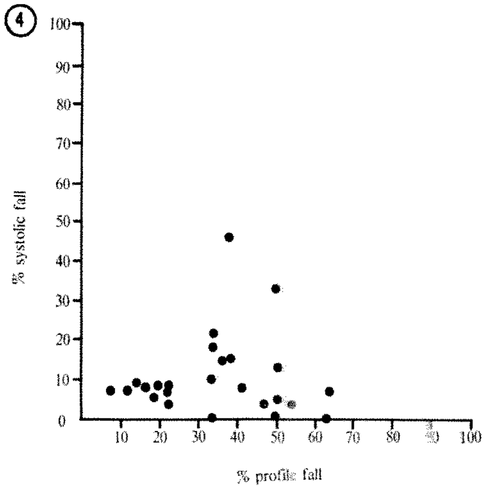


Fig. 2. Blood pressure before and after alpha adrenergic blockade.

Fig. 3. Blood pressure before and after beta blockade.

In the first group of 25 patients who received an alpha blocking drug, phentolamine, there were 21 women and 4 men. Their ages ranged from 19 to 71 with an average age of 46·8. Their diagnoses are a representative sample of the kind of patients attending this department for urodynamic assessment (Table I). 2 control profiles were taken before blockade and then 4 min after the administration of phentolamine 2 more profiles were taken.



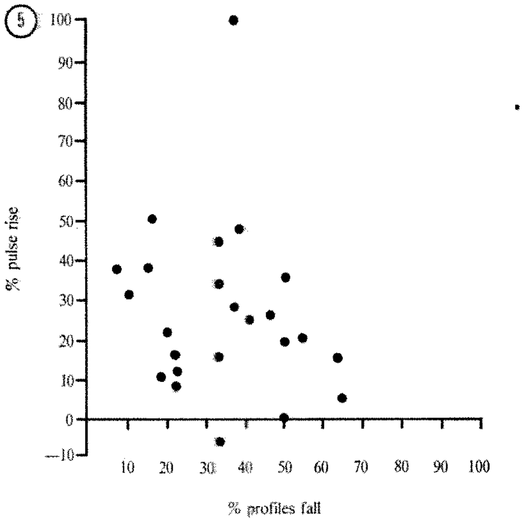


Fig. 4. Graph of percentage systolic blood pressure fall and percentage profile fall after alpha blockade.

Fig. 5. Graph of percentage pulse rise and percentage profile fall after alpha blockade.

In the group of patients who received a beta-blocking drug there were 9 women and 1 man. Their ages ranged from 38 to 55 with an average age of 46·2. Their diagnoses were similar to those in the alpha-block group (Table II). 2 control profiles were taken followed by 2 profiles at 2-minute intervals after the administration of propranolol.

Results

Alpha Blockade. The mean profile height in the 25 patients before alpha blockade was 56·9 cm H_2O (±S.D. 20·3) and the mean profile height after blockade was 36·8 cm H_2O (±S.D. 15·5), which represents a mean percentage fall of 31·9%; this figure is statistically significant ($t = 7·83$, $P < 0·0005$). A typical chart in which a fall in profile of 20 cm water is shown (Fig. 1).

The mean blood pressure before blockade was 135/70 which fell to 120/60 after blockade (Fig. 2). The pulse rate rose from a mean value of 77·4 per min (±S.D. 15·4) before blockade to a mean value of 95·7 per min (±S.D. 21·5) after blockade. No E.C.G. changes were seen.

Beta Blockade. The mean profile height in the 10 patients before beta blockade was 66·1 cm H_2O (±S.D. 19·1) and after blockade was 65·7 cm H_2O (±S.D. 18·1).

The mean blood pressure before blockade was 140/85 which fell to 135/80 after blockade (Fig. 3). The pulse rate fell from a mean value of 82·8 per min (±S.D. 7·3) before blockade to 62·8 (±S.D. 4·6) after blockade. No E.C.G. changes were seen.

Discussion

Adrenergic blocking drugs have been used in clinical practice in cardiology for a number of years but attempts to define their actions are hampered by incomplete understanding of the pharmacology of alpha and beta receptor function and by the lack of specificity of the blocking drugs themselves which are known to have some adrenergic stimulating effects in addition to their blocking action. The primary cardiovascular effect of alpha blockade is to cause a reduction in blood pressure due to peripheral vasodilatation and in response to the blood pressure fall there is a compensatory tachycardia. Beta blockade lowers the resting heart rate, stroke volume and minute output by reducing the sympathetic drive to the heart. Acute administration causes bradycardia and may also cause hypotension in patients with high resting cardiac outputs. Any useful effect of alpha and beta blocking drugs on outflow resistance must be balanced against these cardiovascular effects.

A significant fall in outflow resistance has been demonstrated following alpha blockade at a dosage which does not produce untoward cardiovascular effects. However, there was no correlation between the percentage blood pressure fall (Fig. 4) or the percentage pulse rise (Fig. 5) and the percentage profile fall. This was a surprising finding, since, though we may have failed to produce complete alpha blockade at the dose administered, and though the degree of sympathetic activity might have varied from patient to patient, the degree of alpha blockade produced might have been expected to be reflected equally in the blood pressure fall, the pulse rise and the pressure profile fall. There is no doubt, however, that a significant block was produced as evidenced by the blood pressure fall.

The dose of propranolol used for beta blockade was small but, nevertheless, produced cardiovascular changes of a similar order of magnitude to those seen after alpha blockade and at this dosage the profile height was not affected. It may be that larger doses would have produced some change in profile height but these changes would have been accompanied by more marked cardiovascular effects which would have precluded its clinical use. An alternative explanation would be that in man there is a greater preponderance of alpha receptors at the bladder neck so that beta effects are masked.

Whether the changes in profile height seen after adrenergic blockade are a reflection of a direct effect of blocking drugs on urethral smooth muscle or the reflection of changes solely on the vascular bed of the urethra remains in dispute (Raz and Caine, 1972; Tangaho, Meyers and Smith, 1969). Recent work by Tulloch (1974) has shown that the effects of angiotensin on the urethra are mainly due to its direct action on smooth muscle in the urethral wall rather than to blood pressure changes in vessels of the urethral wall.

A study in 5 female volunteers has shown that a fall in urethral pressure profile following alpha blockade could be reversed by alpha stimulation (Donker, Ivanovici and Noach, 1972). We have confirmed the finding of a fall in profile height following alpha blockade and have shown that such changes occur at much lower doses than they employed. We have failed to confirm in humans the findings of Raz, Zeigler and Caine in dogs that beta blockade causes an increase in profile height.

Conclusions

Alpha blocking drugs may have a useful role in the treatment of patients with increased outflow resistance due to a neuropathic bladder, occult neuropathic bladder or idiopathic retention. On the evidence presented, beta blocking drugs would seem to have no place in the treatment of disorders such as pure stress incontinence in which it is desirable to produce an increased outflow resistance.

Summary

Alpha blockade at a dose which produces minimal cardiovascular effects causes a significant fall in the urethral pressure profile in man.

No change in profile height has been seen following the administration of a beta blocking drug in a dose producing cardiovascular changes of a similar order of magnitude.

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Flat Carcinoma *in situ* of Bladder

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The increasing practice of endoscopic mucosal biopsy from unstable-looking areas of bladder epithelium has produced a dilemma in treatment when the changes of carcinoma *in situ* are unexpectedly found.

Much of the difficulty arises because the term carcinoma-*in-situ* is often used in 2 different contexts—the one describing the pathological stage of a non-invasive papillary tumour and the other denoting a specific type of lesion which is neither papillary nor invasive and is sometimes localised and sometimes diffuse within the bladder. The latter is recognised by the cystoscopist as a patch of mucosal granularity, roughening or reddening and by the pathologist as an area where there are certain characteristic cellular abnormalities in an epithelium which may be of normal or only slightly increased thickness. This second type of lesion is best described as "flat carcinoma *in-situ*". It appears to behave unpredictably and quite differently from the well-differentiated papillary T1 tumour, which usually carries a good prognosis but will almost certainly reappear at varying intervals for the remainder of the patient's life. It must also be distinguished from those tumours that are usually invasive from the start and often poorly differentiated and where the patients usually present with a shorter history and in whom the tumour may already be in the clinical stages T2, T3 or T4 at the time of assessment.

The purpose of this communication is to consider the presentation and management of flat carcinoma *in situ* of the bladder, as a separate entity, as defined by the U.I.C.C. (Wallace, Chisholm and Hendry, 1975) and described as "flat intraepithelial neoplasia" by Barlebo, Sorensen and Ohlsen (1972). The study is based on the collective experience of 36 patients treated at the St Peter's Hospitals (29 patients seen between 1955 and 1974) and Hammersmith Hospital (7 patients seen between 1964 and 1974).

Presentation

It is evident from previous reports that the clinical presentation of the flat *in situ* lesion differs markedly from both that of the papillary non-invasive carcinoma and the invasive tumour (Melamed, Voutsa and Grabstald, 1964; Smith and Badenoch, 1965; Utz, Hanash and Farrow, 1970; Kulatilake, Chisholm and Olsen, 1970; Yates-Bell, 1971; Thelmo *et al.*, 1974).

Similar to other forms of bladder carcinoma the patients in the present series ranged in age from 41 to 79 years; the tumours occurred predominantly in the male and there were only 2 females in the series. The main presenting symptoms in 23 of the 36 patients consisted of dysuria and symptoms of outflow tract obstruction, often in association with haematuria and either penile, perineal or suprapubic pain (Group I). The remaining 13 patients (Group II) presented either with painless haematuria, mild genital discomfort or were detected by positive urine cytology on screening (Table). No patient had a previous history of urothelial tumour and none had been investigated by bladder biopsy or exfoliative urinary cytology before attending our hospitals.

6 patients had undergone prostatectomy more than a year prior to their representation and it is suspected that in some an inflamed bladder mucosa, in association with frequency and urgency, had been thought to be evidence of chronic inflammation secondary to outflow tract obstruction.

Table

Flat Carcinoma *in situ* of Bladder: Presenting Signs and Symptoms in 36 Cases. The Patients in Group I Presented with Multiple Symptoms

		No. of Cases
Group I (23 cases)	± Dysuria	16
	± Obstructive	14
	± Haematuria	9
	± Pain (suprapubic or penile)	7
Group II (13 cases)	Painless haematuria	5
	Pain + haematuria	1
	Pain (dysuria, penile or suprapubic)	5
	No symptoms (cytology positive)	2

In a recent case, the patient underwent a transurethral resection and the diagnosis was made on mucosa obtained from the bladder neck.

The endoscopic appearances vary considerably. An essential feature for the diagnosis is the absence of any other bladder lesion; a high incidence of carcinoma *in situ* and/or epithelial atypia is known to co-exist with bladder carcinoma (Schade and Swinney, 1968). In the majority of the present series there were either colour changes in the bladder mucosa or the mucosa was inflamed, oedematous and described as "cystitis". 3 patients had no specific cystoscopic lesion and a biopsy was carried out only because of the history of frequency and pain.

It is difficult to judge the extent of the *in situ* change without multiple mucosal biopsies. When these were positive or the abnormality was visibly extensive, the history was usually short, the disease progressed rapidly and the prognosis was poor; symptomatically these patients all belonged to Group I (Table). A positive biopsy from a single abnormal area or 1 positive result from multiple areas indicated a lesser degree of change and usually correlated with less severe symptoms and a longer history (Group II, Table). Of the 23 patients in Group I all but 5 had developed an invasive tumour by the time of definitive treatment. Symptoms had been present for from 2 months to 11 years (mean 31 months) and the interval from diagnosis to definitive treatment was on average 10 months, during which time the clinical picture escalated in severity. The duration of symptoms in the 13 patients in Group II ranged from 1 month to 16 years (mean 28 months) and those presenting with painless haematuria were diagnosed within 1 year whereas those with ill-defined "bladder" pain were usually diagnosed only after several years.

While it is acknowledged that routine urine cytological examination is not always available, the value of this technique was a striking feature in the present series. 19 of the 25 cases in which urine cytology screening was carried out proved to be positive. In 4 cases, this led to re-examination of the bladder and subsequent biopsy.

The routine excretion urogram was not usually helpful in this series; however, in 1 patient there was considerable hold-up of contrast at the lower ends of the ureters due to the gross thickening of the bladder mucosa. This patient had widespread carcinoma *in situ* and underwent a radical cystourethrectomy.

Management

The choice of treatment in this series can be directly related to the manner of presentation.

Group I. All patients were treated either by cystectomy or external irradiation:

Cystectomy (12 patients)

1 patient in this group underwent a partial cystectomy but died 2 years later from widespread disease. In the remainder either a simple or radical cystectomy or cystourethrectomy was performed at an interval of between 1 and 24 months

(mean 6½ months) after the diagnosis of flat carcinoma *in situ* had been established. 7 patients were alive at the time of follow-up (5, 4, 4, 2, 2, 1½, ¾ years, mean = 2¾) though 2 have evidence of secondary deposits. 4 patients have died, (6½, 4½, 1, 1 year, mean = 3¼ years) of disseminated disease.

Adequate pathological material was available from 11 of the 12 operation specimens and in all but 2 very extensive neoplastic changes were found. All 11 had areas of flat carcinoma *in situ*; in 4 there was unsuspected papillary and solid carcinoma (with evidence of infiltration of the lamina propria) and in 5 there was also solid carcinoma, without any papillary element but with evidence of infiltration of the lamina propria in 3 specimens and of the deep muscle in 2. One tumour was of squamous type and the other 10 were transitional cell carcinomas. All but 2 were of an anaplastic grade.

External Irradiation (11 patients)

Only 1 patient in this group is alive at 18 months; the histology has remained unaltered. There was a suicide at 1 year (the patient complained bitterly of perineal pain) and 1 patient died at 3 years from gastrointestinal complications of radiotherapy (there was no tumour in the bladder but metastases were present in the para-aortic lymph nodes). 7 of the remaining 8 patients died of their disease at 1, 1½, 2, 3, 5, 6½, 7 years (mean 3½ years); the 8th patient was found to have a carcinoma of the prostate 2 years after radiotherapy and died 4 years later from this second malignancy.

Group II. The treatment of patients in this group was more varied:

No treatment

6 patients have been maintained under close observation but have not received specific treatment. One patient has died 7 years later with "liver metastases"; exact details are not known. Another patient died from a myocardial infarct after 2 months. The remaining 4 patients are well and asymptomatic (6 years, 3 years, 2 years and 3 months).

Intra-cavity Cytotoxic Treatment

4 patients have been treated with Epodyl; all are alive at 2 years, 2 years, 1 year and 6 months after diagnosis.

Radium Needles and Local Excision

1 patient had an apparently localised lesion behind the left ureteric orifice. The area was excised and radium needles were inserted for 6 days. He has remained well, with no sign of recurrence for 12 years.

Excision of Diverticulum with in situ *Lesion*

1 patient underwent a retropubic prostatectomy and diverticulectomy; an *in situ* bladder tumour was localised in the dome of the diverticulum. The patient has remained symptom free for 6 years.

Cystodiathermy

1 patient who had worked for a rubber company was asymptomatic and was found to have abnormal cytology on examination of the urine. A single 1 cm diameter "red patch" was biopsied and diathermised. Although there are no longer any visible lesions he continues to have abnormal cells in the urine after 1 year and is under close observation.

Discussion

The histopathological definition of carcinoma *in situ* of the urinary tract has been discussed by many authors (Melicow and Hollowell, 1952; Melamed *et al.*, 1960, 1964; Pugh, 1973) but no rigid criteria for its diagnosis have yet been established.

The malignant potential of the lesion originates from observations that bladder epithelium showing full thickness epithelial atypia on histological examination has been seen in biopsies before the onset of invasive cancer and in epithelium adjacent to such a tumour (Schade and Swinney, 1968).

In the prospective situation, however, there is debate among histopathologists concerning which epithelial abnormalities indicate precancer. In the cases under review histological examination of the biopsy fragments showed severe degrees of epithelial atypia consisting of replacement of the whole thickness of the epithelium by large pleomorphic cells, many of which showed mitotic activity in the intermediate and superficial layers. In addition, there was often marked stromal vascularity and a non-specific inflammatory cell infiltration.

The lack of cohesiveness observed in the epithelial cells of the the biopsy fragments is reflected in the large number of cases in which cytological examination of the urine revealed cancer cells. In many cases this was the first indication to the urologist of the true diagnosis. However, contrary to some workers (Voutsa and Melamed, 1963) we are unable to report any specific differences between cells exfoliated from flat carcinoma *in situ* and those shed from an invasive lesion.

In this retrospective study of 36 patients with flat carcinoma *in situ* of the bladder, a clear pattern of presentation and management has emerged. In those 23 patients presenting with either pain, obstruction or the symptoms of cystitis, there was evidence of widespread disease within the bladder (Group I). At the time of definitive treatment, all but 5 had become invasive as shown either by the biopsy or the cystectomy specimen. It is not difficult to imagine that had they not been treated, all would have developed disseminated disease. However, we have no comparable series that has not been treated to act as a control.

The decision for either cystectomy or external irradiation has not always been made on rational grounds. Many urologists have been unwilling to subject their patient to major surgery for an apparently early stage disease. Similarly, some patients have not accepted the advice for radical excision. In such circumstances, external radiotherapy has been used as a compromise. It is probably too early to make a fair comparison between the radiotherapy and cystectomy groups in this series. Only 1 patient treated by radiotherapy remains alive whereas 7 are alive after cystectomy. However, the follow-up periods are different. It is evident that radiotherapy has in no way prevented dissemination whereas it is possible that a substantial proportion of those treated by cystectomy will remain tumour-free.

In those patients presenting with haematuria, sometimes associated with genital discomfort, or positive urine cytology only (Group II) the disease was localised and a more conservative approach has been adopted. It would appear a correct decision to continue to observe closely a patient with only a small area of bladder involved with *in situ* change. Regular biopsies should give an early indication of any alteration in the histological pattern.

4 patients have been treated with a course of Epodyl. These patients remain well and symptom free but the follow-up does not extend beyond 2 years.

Diathermy or local removal has been used in the treatment of 3 patients. These patients remain alive and well and it may be presumed that their *in situ* change affected only a small localised area in the bladder.

Summary

36 patients with flat carcinoma *in situ* of the bladder have been reviewed.

Those with widespread disease usually presented with dysuria or obstructive outflow tract symptoms and radical surgery appeared to give better results than radiotherapy. However, when the lesion was confined to small areas of the bladder mucosa, haematuria or pain were the main presenting symptoms and a conservative approach seemed justified.

It is suggested that the term flat carcinoma *in situ* be used for this lesion whose behaviour differs significantly from that of the commoner papillary or invasive tumours. The pathological appearances are to be reported elsewhere in full.

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The Effects of Overstretching on the Structure and Function of the Bladder in Relation to Helmstein's Distension Therapy

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The original experimental observations of Mehrotra (1953) in the rat showed that prolonged overdistension of the bladder led to mucosal and intramuscular haemorrhage. One would expect this to be succeeded by fibrosis and, perhaps, by a reduction in the capacity of the bladder. We were therefore interested in the suggestion of Lloyd-Davies and Hinman (1971) and Mayo *et al.* (1973) that overdistension of the bladder might be followed by atonia and that the syndrome of the large floppy bladder associated with a large residual urine might be the consequence of retention of urine. It seemed of some importance to find out what had happened to the capacity and motility of the bladder in our patients who had undergone Helmstein's distension treatment (Helmstein, 1966, 1972).

Material and Methods

In the series of patients treated by distension therapy there were 73 in whom the procedure could be said to have been carried out according to Helmstein's original recommendations, and in whom the period of distension was adequate and the anaesthetic satisfactory. A number of cases were rejected for the purposes of this study since the pressure in the bladder was inadequate or the period of therapy curtailed because of want of analgesia. Details of the method in current use have been described by England *et al.* (1973). A specially designed rubber balloon was used in the majority of these cases.

Bladder distensibility has been used to denote the volume of fluid which was run into the balloon during the period of treatment, a volume far greater than the "normal" bladder capacity. *Cystometrography* was performed using a 6 Ch catheter introduced under local 1% xylocaine anaesthesia with a constant filling rate of 100 ml/min and a transducer. *Bladder biopsies* were taken with cup forceps at cystoscopy, or at the time of cystectomy.

Patients in this series fell into 3 main groups: (*a*) when Helmstein treatment was used as the primary method of therapy after initial cystoscopy and biopsy (38 cases); (*b*) where Helmstein therapy was used after multiple previous cystoscopic biopsies, resections and diathermisations had been carried out, or open cystodiathermy and gold grain implantation had been performed (11 cases); (*c*) where Helmstein treatment was used after previous radiotherapy: there were 19 such cases, 17 with post-radiation haemorrhage and 2 with recurrent tumour.

3 of the cases who were at first treated by Helmstein's method were subsequently given radiotherapy for recurrent tumour and in 11 patients more than 1 treatment by Helmstein's method was carried out; in 7 of these it was for recurrent tumour and in 4 because of recurrent post-irradiation bleeding.

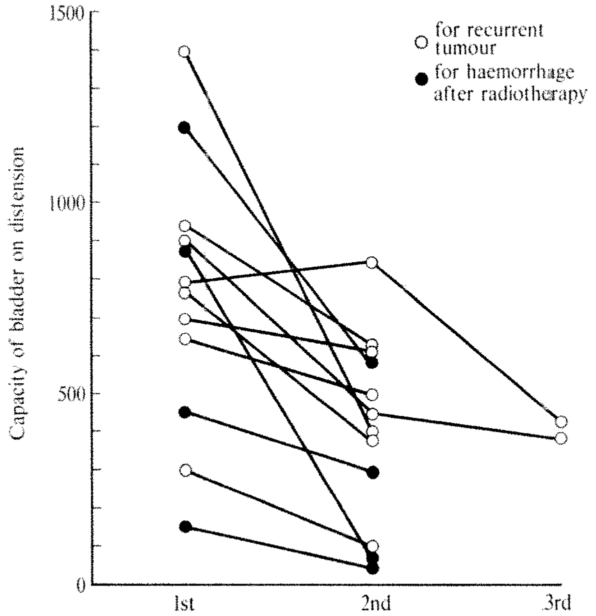

Fig. 1. Graph showing progressive diminution of the maximum distensibility of the bladder with successive Helmstein treatments.

Results

Bladder Distensibility (Fig. 1)

In all cases where a second Helmstein treatment was attempted, the bladder distensibility, *i.e.* the maximum volume of fluid which could be introduced into the balloon, had been reduced.

This was particularly marked in patients where the distension treatment had been carried out after previous radiotherapy: in 11 of these patients the maximum distensibility was less than 500 ml and in 1 patient the bladder had shrunk to 75 ml.

When radiotherapy was given *after* Helmstein's therapy severe bladder contracture occurred in all 3 cases and indeed necessitated urinary diversion in 2 of them.

Repeated Helmstein therapy was accompanied by further reduction in the distensibility of the bladder, a reduction which was most marked in those cases in whom there had been previous radiotherapy.

Cystometrographic Findings

Cystometrography was performed in 10 of the patients in whom Helmstein's therapy had been used without previous radiotherapy or surgery on the bladder. In 4 cases the capacity was reduced (*i.e.*, the volume at which discomfort was noted or at which voiding occurred around the catheter) and in these cases there was evident detrusor irritability. In 2 patients only was there a large capacity bladder and in both of these there had been previous outflow obstruction from enlargement of the prostate: both of these patients had normal sensation and detrusor contractions. 1 patient was studied after radiotherapy and Helmstein treatment: the capacity was limited to 275 ml and the detrusor was noted to be irritable.

In 1 patient, with a small bladder capacity and a supposed Hunner's ulcer, distension therapy was carried out in the hope of relieving her symptoms. Cystometrograms before and after treatment were unchanged.

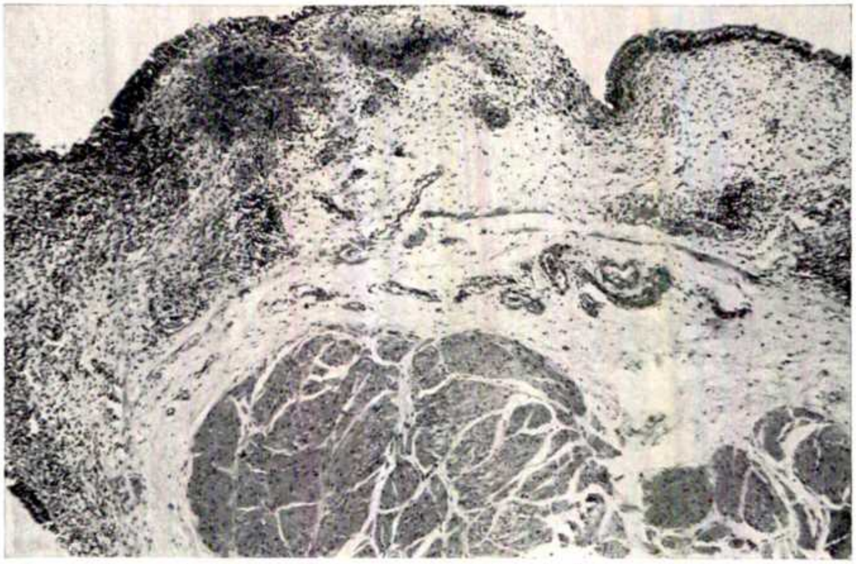

Fig. 2. Biopsy of bladder wall 6 weeks after Helmstein therapy, showing submucosal haemorrhages and lymphocyte infiltration. Muscle shows little change. H & E. × 10.

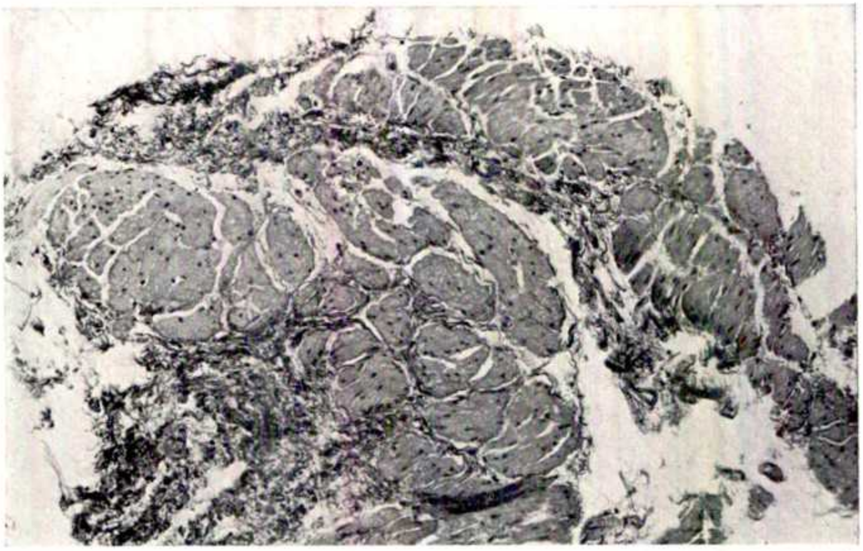

Fig. 3. Biopsy of bladder wall 15 months after Helmstein therapy, showing bladder muscle partly replaced by collagen. H & E. × 7.

Far from encountering any cases with large atonic bladder, none of those which were studied by cystometrography showed any residual urine greater than 50 ml.

Microscopic Findings

Light microscopy in 5 patients in whom Helmstein's therapy had been performed without previous surgery or radiotherapy showed submucosal haemorrhages and lymphocytic infiltration with

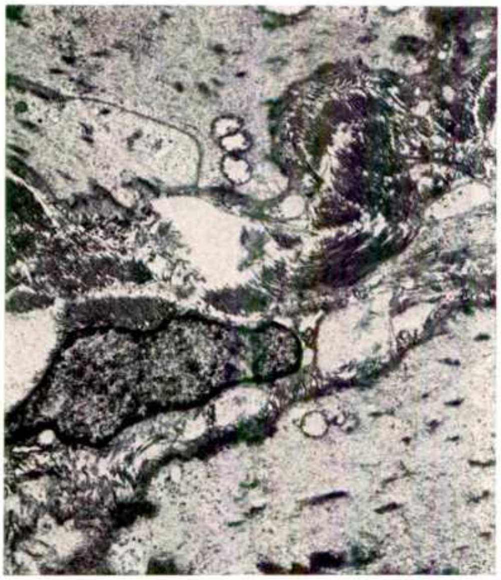

Fig. 4. Bladder wall 6 weeks after distension, showing smooth muscle cells separated by oedema and collagen fibrils. One fibroblast present. (Uranyl acetate and lead citrate. ×4,500.)

little change in muscle at 6 weeks (Fig. 2). 1 year later there was more extensive replacement of muscle fibres by collagen (Fig. 3). Electron microscopy at 6 weeks showed mainly intact smooth muscle cells, separated by oedema and a few collagen fibrils (Fig. 4) but at 15 months there was evidence of further smooth muscle cell damage and extensive formation of collagen (Fig. 5).

Discussion

Although Helmstein's distension therapy is only applicable to a limited number of cases with bladder tumour or post-radiation bleeding, nevertheless, in these patients it can avoid the need for open diathermy removal of the tumour or the considerable hazards of emergency cystectomy for uncontrollable bleeding. In these particular patients it can be most valuable and consequently the method is being used increasingly often (England *et al.*, 1973; Glashan, 1975). Nevertheless it is important that urologists should be aware of the pathological changes which must follow upon such overdistension of the bladder. As Mehrotra (1953) originally showed in the rat, interstitial and submucosal haemorrhages occur during the period immediately after distension and indeed this can be observed on cystoscopy after the balloon is removed. These haemorrhages are bound to be followed by fibrosis and it is only to be expected that the bladder will not be capable of being overstretched on a second or third occasion, at least to the same extent. Since the effect of previous surgery and more especially of previous radiotherapy must be to lay down fibrous tissue in the wall of the bladder, it is not surprising that an even more marked contracture of the bladder occurs when Helmstein therapy is used before or after these additional forms of treatment. When repeated bleeding after previous radiotherapy requires repeated use of the Helmstein balloon, then one should be prepared to consider urinary diversion and perhaps the cautious use of hyperthermic irrigation (England *et al.*, 1975).

We have been particularly concerned at the suggestion that distension of the bladder might lead to atony. Nothing in everyday urological experience with retention of urine from prostatic enlargement would lead one to expect this result and nothing in the results presented here would support the notion. It could be argued that the kind of distension which follows acute retention of urine, where the intravesical pressure rises to perhaps as much as 32 cm H_2O, is quite different from the distension used here, where the intravesical pressure is 3 to 4 times as high. Nevertheless,

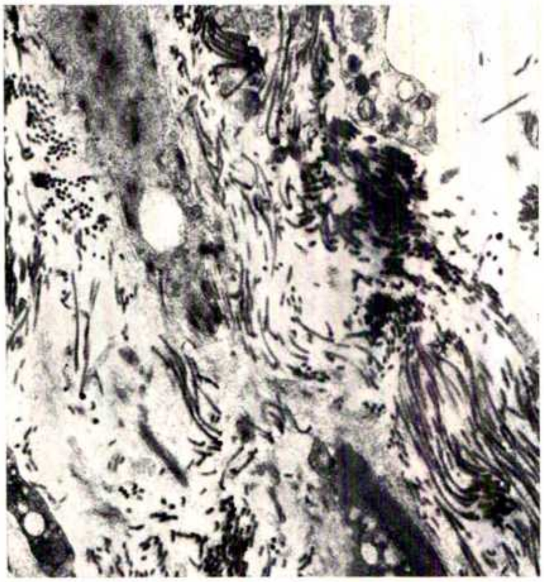

Fig. 5. Bladder wall at 15 months showing necrotic muscle cells with extensive collagen between them. (Uranyl acetate and lead citrate. × 11,250.)

the pathological consequences of distension, *i.e.* the deposition of collagen fibres in amongst the muscle of the bladder wall, whether detected by light or by electron microscopy, would be expected to restrict the distension of the bladder rather than augment it. It may well be that it is time to question the popular concept that "stretching" will lead to atony in the context of an acute distension rather than the chronic dilatation seen with chronic outflow obstruction.

Summary

Measurements of the maximum bladder distensibility, cystometrograms and histological studies of the bladder after Helmstein's distension therapy show intramural fibrosis and a reduction in bladder capacity. When this is made worse by post-radiation fibrosis it may give rise to such severe contraction that diversion may be needed. There is no evidence that distension, of the type used here, ever gives rise to "stretching" or "atony" of the bladder: and it is questionable whether distension of a lesser degree, such as may be found in acute urinary retention, ever does so either.

We are grateful to Mr W. R. Russell-Fell of the London Rubber Company for his continual help in the design and supply of the special balloons used in this work.

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Hyperthermic Perfusion of the Distended Urinary Bladder in the Management of Recurrent Transitional Cell Carcinoma

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Temperatures above 40°C have been shown by *in vitro* and animal studies to be selectively lethal to cancer cells (Cavaliere *et al.*, 1967; Dickson and Shaw, 1972). Hyperthermic therapy in man has either taken the form of isolated limb perfusion for localised disease (Stehlin *et al.*, 1975) or whole body hyperthermia for disseminated disease (Pettigrew *et al.*, 1974). Local hyperthermia may have a role in treatment of transitional cell carcinoma of the urinary bladder since the disease tends to remain localised and spreads mainly by local invasion. In view of the discouraging results following total cystectomy for invasive carcinoma (Whitmore and Marshall, 1962) and the ease with which local hyperthermia can be induced by perfusion, it is not surprising that several attempts of this form of treatment have been made. Local hyperthermic irrigation through a 3-way Foley catheter has been used either alone (Hall, Schade and Swinney, 1974) or to enhance the effects of radiotherapy (Cockett *et al.*, 1967), or chemotherapy (Lunglmayr *et al.*, 1973). In each of these studies the undistended urinary bladder has been perfused. In the contracted state the bladder forms folds of mucosa which might shield the tumour from the full effects of hyperthermic perfusion. This is a report of 13 patients with transitional cell carcinoma of the bladder, recurrent following radical radiotherapy, treated by hyperthermic perfusion of the distended urinary bladder. Most presented with cross haematuria not controlled by repeated local cysto-diathermy.

Method

15 treatments were carried out in 13 patients. It was found that even slight bladder distension proved uncomfortable and because of the variation in flow rate due to bladder contraction the temperature was difficult to control. Continuous epidural anaesthesia allowed relaxation of the bladder and a steady flow rate to be achieved at a constant temperature.

Under epidural anaesthesia the nature and extent of the tumour was established by cystoscopy and bimanual examination. Biopsies were taken from the tumour and from the normal bladder mucosa. The bladder capacity was measured and a 24 F 3-way Foley catheter introduced into the bladder and inflated with 5 cc of warm saline. The bladder was then washed out to remove air bubbles and perfused with normal saline which was heated by passing through a heating coil inserted in the water bath. The outflow ascended a gradient to an overflow tank (Fig. 1), the height of which was adjusted so that slightly less than the known bladder capacity caused overflow. This was usually at a height between 15 to 20 cm above the symphysis pubis. The patient was placed on an X-ray table during treatment and the degree of distension was monitored radiographically by injecting a coloured solution or radio-opaque medium into the perfusate and taking check films. Thermo-couples were used to measure the inflow, outflow and rectal temperatures. A further probe was attached to the skin 1 inch above the symphysis pubis (Fig. 1). It is hoped that a further probe, when it is available, will be introduced into the tumour itself to determine

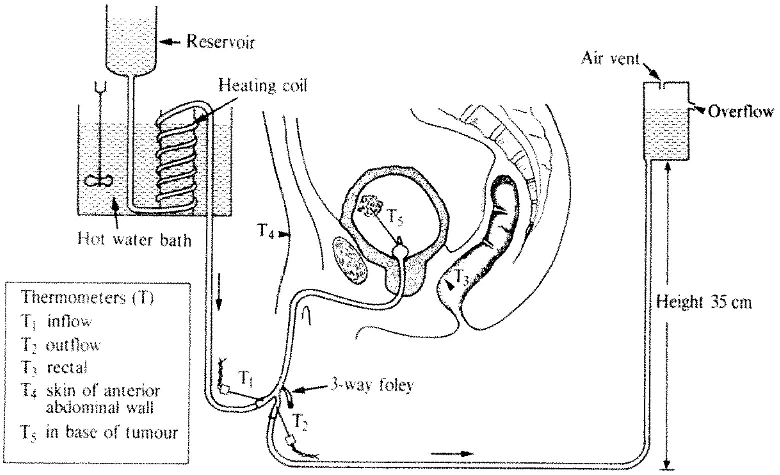

Fig. 1. Method of hyperthermic perfusion of the distended bladder. The overflow height was approximately 35 cm above the table or 15 to 20 cm above the symphysis pubis.

whether the outflow temperature truly reflects the temperature of the tumour. Perfusion was at a constant rate of 3 litres per hour, the inflow temperature being adjusted to give the required outflow temperature. It was initially intended to use an outflow temperature of 45°C (Hall *et al.*, 1974) but this caused lower abdominal discomfort and the temperature was therefore reduced to 44°C, which was well tolerated by all patients. 3 patients were treated at an outflow temperature of 43°C for 4 hours. At the beginning of the perfusion there was a rapid rise in the outflow temperature which remained stable provided that the inflow temperature was kept constant (Fig. 2). The rise in skin and rectal temperatures depended to some extent on the size of the tumour. It was greatest when the tumours were infiltrating and extensive, rising to 40·5°C in such cases, during the first 2 hours of treatment.

At the end of the treatment session a Foley catheter was inserted and left on free drainage for 24 hours before removal. The effect of the treatment was assessed by cystoscopy, bimanual examination and biopsies. These were initially taken 3 days and 2 weeks after treatment and thereafter at 6-weekly intervals. In later cases biopsies were also taken immediately at the end of treatment.

Results

The duration of perfusion varied from 1 to 4 hours. In all cases gross haematuria was arrested but slight haematuria persisted for up to 1 week following treatment. After treatment of 1 hour's duration there was no frequency. At cystoscopy the mucosa appeared healthy and the bladder capacity was not altered but there was residual viable tumour present. These 2 patients had recurrent haematuria at 6 weeks and required further treatment (Table).

After 3 hours at 44°C there was obvious tumour necrosis appearing at cystoscopy as a grey-white slough which took up to 2 months to separate from the mucosa. The normal mucosa appeared red and inflamed and the bladder capacity was reduced to between 150 to 200 ml. There was no evidence of recurrent tumour for 3 months. Thereafter, recurrence was found in 3 of the 6 patients (Table).

After 4 hours at 44°C there was prolonged and continuing frequency and at cystoscopy the bladder capacity was reduced to between 50 to 75 ml. The whole of the bladder mucosa was covered by a grey-white slough. Bimanual examination revealed an indurated palpable bladder.

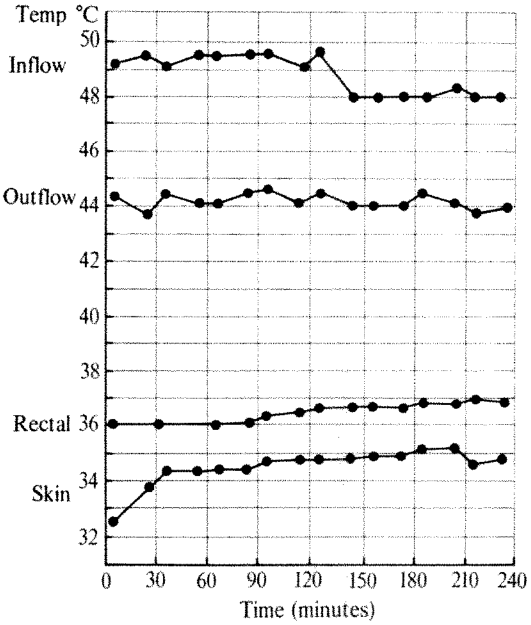

Fig. 2. Temperature graph during treatment.

No recurrent tumour has been found in this group at 6 months but, because of continued frequency, urinary diversions became necessary. They remain well at present with no tumour recurrence (Table).

Histopathology

The tumour biopsies taken before hyperthermia were graded as described by Bergkvist, Ljungquist and Moberger (1965). 6 tumours were Grade II, one of which was invasive; 6 were Grade III, 5 of which were invasive and 1 was Grade IV and invasive.

The effects of hyperthermia on the bladder vary according to the interval after treatment. Changes seen in the transitional cell at the end of the treatment session consisted of nuclear vacuolation, pyknosis, with vacuolation of the cytoplasm, and reduction of epithelial adhesion. These early changes were similar to those reported in the epidermis after thermal injury (Moritz,

Table

Local Bladder Hyperthermia: Comparison of Clinical Results following Different Temperature/Time Combinations

Outflow temp. (°C)	Treatment time (hours)	Duration of frequency (weeks)	effect on tumour
44	1	Nil	Nil
44	2	1	Nil
44	3	12	Clear 3/12
44	4	20+	Clear 5/12+
43	4	6	Some necrosis

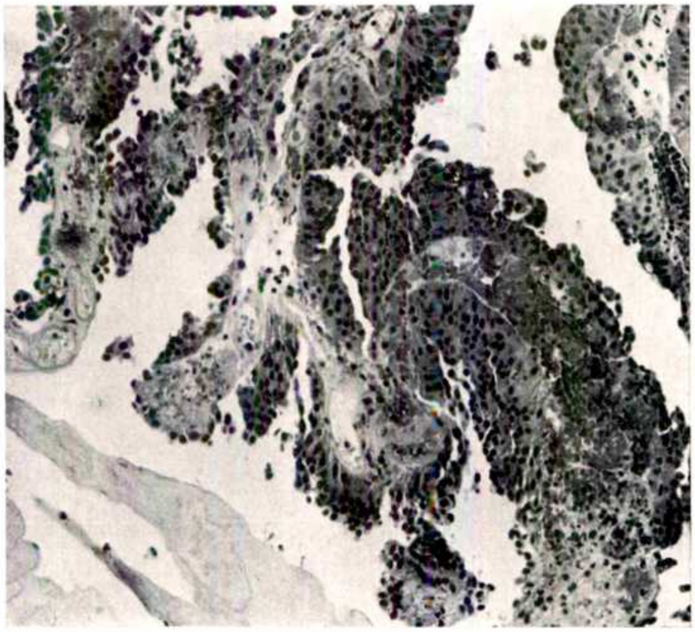

Fig. 3. Necrosis in bladder tumour immediately after treatment for 3 hours at 44°C. Some villi are ghost-like (bottom left). In the central villi, stomal haemorrhage is accompanied by partial necrosis. The remaining villus and its stroma are relatively normal. H.E. × 180.

1947). Slight changes, however, were not easy to assess in a bladder which was inflamed following hyperthermia and had previously been subjected to radiotherapy and repeated cystodiathermy. Severe effects were easily recognised in both tumour and mucosal epithelium and were often accompanied by vascular and connective tissue changes.

Effect of Hyperthermia on Bladder Tumour

No tissue necrosis was seen in tumour biopsies taken after 1 hour's perfusion at 44°C. The effects seen in biopsies taken at the end of 3 to 4 hours' perfusion were often patchy, one part of the tumour showing little change whilst another showed complete necrosis. Necrotic areas were accompanied by local vascular changes such as necrosis and thrombosis in the small vessels of the tumour and haemorrhage into its stroma. These vascular changes may be responsible for some of the tumour destruction since blood vessels are more susceptible to thermal injury than is normal epithelium (Moritz, 1947). Necrosis manifested itself in 2 main forms, either as ghost-like villi or in disintegration of the tumour with disruption of its cells (Fig. 3). 3 days after perfusion for 3 to 4 hours, necrosis was usually so advanced that it was difficult to recognise tumour in the biopsy material.

3 of the tumours recurred 2 months or more after hyperthermia. 1 was a Grade II tumour (Bergkvist *et al.*, 1965) and 2 were Grade III tumours. Both of the Grade III tumours appeared invasive before and after treatment.

Effect of Hyperthermia on Bladder Mucosa

The normal mucosal epithelium initially was considerably less affected than the tumour. Quite marked changes, however, occurred in the blood vessels and connective tissue of the mucosa and these led to additional changes in the epithelium.

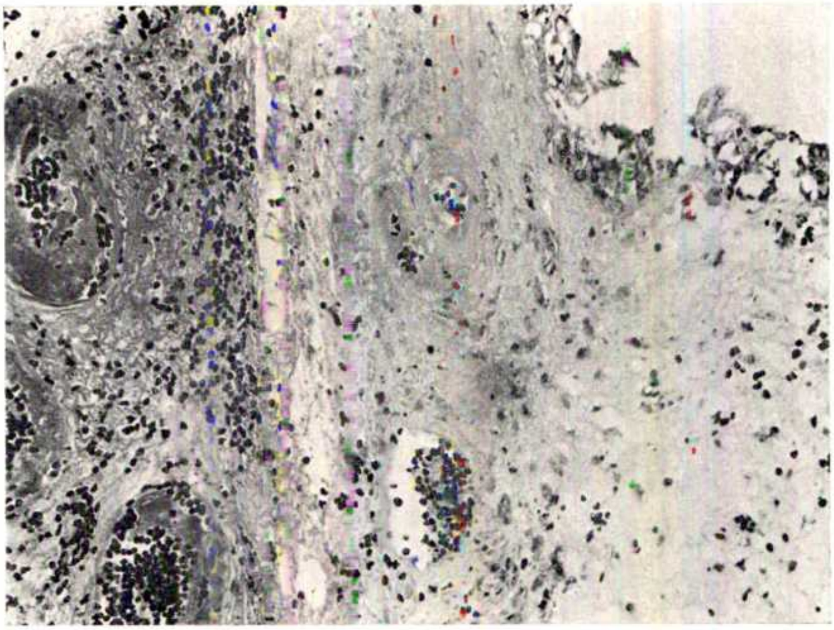

Fig. 4. Bladder mucosa 3 days after 44°C for 4 hours showing vascular necrosis and haemorrhage with devitalisation of stroma and disintegration of transitional cell epithelium. H.E. ×250.

Hyperthermia resulted in congestion and oedema of the lamina propria with inflammatory cell infiltrate sometimes including numerous eosinophils. Thermal effects upon blood vessels of the mucosa led to exudation of plasma and sometimes to interstitial haemorrhage. Some of the vessel walls were frankly necrotic (Fig. 4) and thrombi tended to form (Fig. 5). These vascular changes exacerbated the direct thermal injury of the lamina propria, sometimes resulting in areas of necrosis with exfoliation of epithelium and subsequent formation of hypervascular inflamed granulation tissue. A degree of fibrosis usually followed (Fig. 6). Regeneration of epithelium was obvious in the biopsies taken 2 months after hyperthermia but may have been established sooner.

Discussion

The aim of local hyperthermic treatment of transitional cell carcinoma of the bladder is to cause maximal tumour damage with minimal injury to normal tissue. In this, the method was only partly successful. Distension of the urinary bladder during hyperthermic perfusion ensured that all the papillary tumour was exposed to the perfusing fluid. Continuous epidural anaesthesia prevented intermittent bladder contraction which had previously caused fluctuation in flow rate and difficulty in maintaining a constant temperature. The procedure is simple and was well tolerated by all patients.

Perfusion at 44°C for 3 or 4 hours or at 43°C for 4 hours resulted in tumour necrosis but prolonged perfusion at the higher temperature was followed by frequency of micturition and bladder contraction. This has been found in previous reports (Hall *et al.*, 1974) and may be due to exposure of the whole epithelium or sensitisation by previous radiotherapy. There have been no urinary symptoms following whole body hyperthermia at 41·8°C for up to 11 hours. At temperatures above 42°C there was some damage to normal cells (Pettigrew *et al.*, 1974). In tissue culture experiments some He La cells survive 25 hours' exposure at 42°C; exposure at 43°C produced

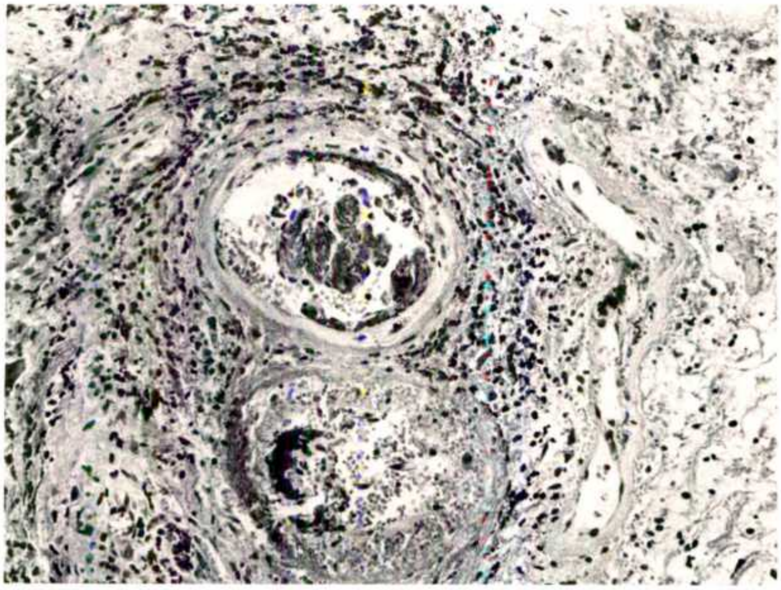

Fig. 5. Bladder mucosa 3 days after 44°C for 1 hour showing non-occlusive thrombi in deep vessels. MSB. × 180.

considerably more cell destruction, few cells surviving 2 hours at this temperature (Palzer and Heidelberger, 1973). The effect of hyperthermia on human and animal tissues is doubled for each 1°C rise in temperature (Moritz, 1947). In the present investigation hyperthermic perfusion for 1 hour at 44°C was not followed either by bladder irritability or by appreciable tumour necrosis. The effect of longer perfusions resulting in tumour necrosis appeared to be brought about not only from a direct action on the tumour cells but also from injury to its blood vessels. This latter mechanism was probably responsible for damage to the bladder mucosa. In the skin, Moritz (1947) has shown that dermal vessels are far more responsive to temperature changes than are normal epithelial cells, and that severe and persistent vascular reactions were often elicited by protracted episodes of hyperthermia of low intensity that fail to harm the epidermis. If this pertains to the bladder it will be a factor limiting the prolonged treatment of tumours deeply infiltrating the bladder wall or surrounding tissue. To achieve a therapeutic effect it is necessary to raise the temperature of an infiltrating tumour to a minimum of 40°C. Prolonged perfusion at 44°C has been shown to produce this temperature in the rectum in the case of extensive tumours infiltrating the bladder base.

Hyperthermic perfusion of the bladder at relatively low temperatures results in necrosis of transitional cell carcinomas and freedom from tumour which may persist for several months. Our results and those of previous workers (Hall *et al.*, 1974) suggest that invasive tumours tend to recur early. Much work needs to be done in terms of sensitivities, fractionation and temperature gradients to assess the role of this method in the treatment of bladder cancer. This preliminary investigation has, however, shown that the method is of value in arresting intractable haemorrhage. Fractionated therapy, at a lower temperature, may cause a selective lethal effect upon the tumour cells without damage to the deeper vasculature of the bladder. It is this possibility which requires further evaluation.

Summary

The clinical and histological changes following hyperthermic perfusion of the distended urinary bladder have been studied in 13 patients with transitional cell carcinoma, persistent after radical

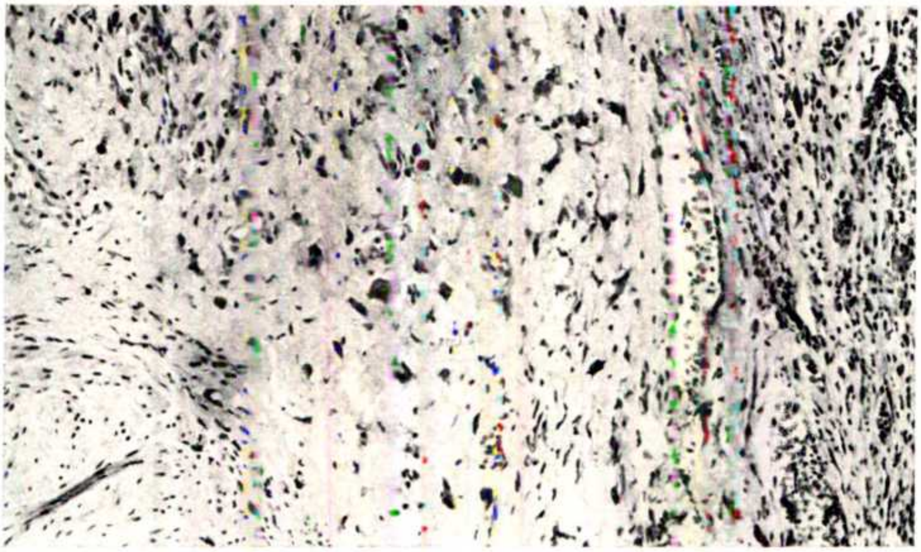

Fig. 6. Fibrosis 2 months after 44°C for 24 hours. The bladder surface is seen bottom right and the muscularis bottom left. H.E. × 150.

radiotherapy. Continuous epidural anaesthesia was necessary to achieve a constant state of bladder relaxation during irrigation of the distended bladder.

This form of hyperthermic perfusion of the bladder was effective in arresting uncontrollable haemorrhage from bladder tumours and may be of value in the treatment of this complication.

Perfusion at an outflow temperature of 44°C for 4 hours caused tumour necrosis. It was, however, associated with damage to the vasculature of the bladder and frequency of micturition which persisted after mucosal recovery. Perfusion at 43°C also caused tumour necrosis and the after effects were less severe.

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The Therapeutic Application of Hyperthermia in the Bladder

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By irrigating the bladder with hot saline its wall can be heated in an accurate and controlled manner so that, if desired, complete destruction can be obtained. It is this aspect of hyperthermia, and its possible application to the treatment of selected cases of bladder cancer and their complications, which form the basis of this preliminary report.

After first diverting the urine Linke *et al.* (1972) completely destroyed the bladders of female dogs by irrigation for 8 min with water at 85°C. In male dogs the time had to be extended to 15 min because their bladders were thicker and more vascular (Netto, Elbadawi and Linke, 1973). At lower temperatures and with shorter times destruction was patchy and incomplete. The animals remained well and at autopsy after 10 weeks their bladders had become converted to small knots of fibrous tissue. There was no thermal damage to adjacent structures or to the urethra.

We began to use hyperthermia as an adjuvant to Helmstein's distension therapy (Helmstein, 1972); our interest was rekindled when a patient was referred 4 months after having had very hot water introduced into the bladder by accident during cystoscopy. 1 month after the accident her blood urea was 32 mg/100 ml, her urine was uninfected and her upper tracts were dilated down to her bladder, the capacity of which was reduced to 60 ml. The urethra was normal but the ureteric orifices were gaping. A biopsy showed loss of virtually all the epithelium and muscle, with fibrous replacement of these layers. A caecocystoplasty was easy to perform and it was noteworthy that at laparotomy there was no sign of any injury to the adjacent viscera. The clinical course of this patient and the histological changes in the bladder were closely parallel with those reported in dogs subjected to experimental hyperthermia.

9 patients have been treated (Table). 3 of these had T4 tumours with particularly distressing symptoms. 4 others with T1 tumours had intractable haemorrhage, in 2 of whom previous radiotherapy was a contributing factor. Distension therapy had failed to control the bleeding in 3 cases and in 1 had resulted in septicaemia and rupture of a very thin bladder; the other had undergone urinary diversion 2 years previously and for her the procedure was a minor one. 1 patient in this group was offered hyperthermia because he refused to undergo cystectomy when he learned that it would render him impotent. In 2 patients there was residual T1 tumour in a grossly contracted bladder following radiotherapy, and 1 of these also refused cystectomy because of its effect upon his potency.

Method

Diversion was by ileal conduit. This allowed the measurement of the temperature in the peritoneal surface of the bladder during irrigation, as well as in the rectum. In the first 3 patients we used a balloon distended under pressure with the hot saline but afterwards we used a specially designed irrigating system (Fig.), the key feature being a control unit which allowed any temperature between 65° to 85°C for the fluid inside the bladder to be selected. A thermo-couple within the bladder was connected to this control unit. Saline was pumped through a heating coil and into the bladder. An additional safety circuit was incorporated which switched off the heater whenever

Table

Patients Treatment and Results

Case No.	Sex	Age	Remarks	Temp.	Time	Results
1	F	63	Accidental hyperthermia during cystoscopy	?90°C	A few mins.	Destruction of epithelium and muscle
T4 tumour for palliation—Helmstein balloon technique						
2	F	66	Squamous from cervix—radiation + Wertheims, 1961	50°C	120 mins	Worthwhile palliation
3	M	47	Previous 5,000 rads	60°C	60 mins	No improvement
4	M	72	Previous 5,000 rads	50°C	90 mins	No improvement—cystectomy at 6 weeks
Intractable haemorrhage and T1 tumour—irrigating system						
5	F	76	Previous 5,500 rads—failed distension therapy	65°C 80°C	75 mins 10 mins	Tumour eliminated—bleeding stopped, recurred at 4 months. Bleeding controlled
6	M	61	Previous 5,5000 rads—failed distension therapy—refused cystectomy	80°C	15 min	Bleeding stopped—became infected
7	F	61	Ruptured bladder and septicaemia from distension therapy	80°C 80°C	5 min 10 min	Bleeding stopped—residual tumour
8	F	78	Diverted already because of incontinence	80°C	10 min	Bleeding controlled—tumour and epithelium destroyed
Contracted bladder and T1 tumour						
9	M	46	Previous 5,500 rads—refused cystectomy	50°C	60 min	Epithelium and tumour eliminated
10	M	69	Previous 6,000 rads	80°C	15 min	Epithelium and tumour eliminated

its temperature rose 10° above the level selected for the fluid inside the bladder—pilot studies having shown that there was a 10° gradient of heat loss between heater and bladder.

When a balloon was used the heating was continued for 120 min at 50°C, 60 min at 60°C and 90 min at 50°C respectively. Using the irrigating system an intravesical temperature of 80°C was aimed at, with exposure times of 10 min in women and 15 min in men, values which were departed from in 3 cases because of equipment failure in 1, and because of fear of visceral damage in another (a patient with a very thin bladder) and of causing impotence in the 3rd.

After hyperthermia the bladder was irrigated with saline through an indwelling 3-way catheter for a few days.

Results

In the first 3 patients when a balloon and a relatively low temperature was used, only 1 of these T4 patients was improved; subsequent biopsies showed patchy destruction of the epithelium but the deeper tumour and the bladder muscle was untouched.

In those with intractable bleeding and T1 tumours the haemorrhage was readily controlled. In the first of them no tumour could be seen at follow up and the biopsy only showed necrotic tissue but bleeding recurred at 4 months and was stopped by a second irrigation with hot saline. Only slough could be seen on cystoscopy in the second case and no biopsy was taken. In the third, islands of viable epithelium and tumour remained after a treatment which had been terminated at 5 min, while in the last of this group neither tumour nor recognisable bladder tissue could be found on cystoscopy. In the first patient in whom hyperthermia was used in the hope

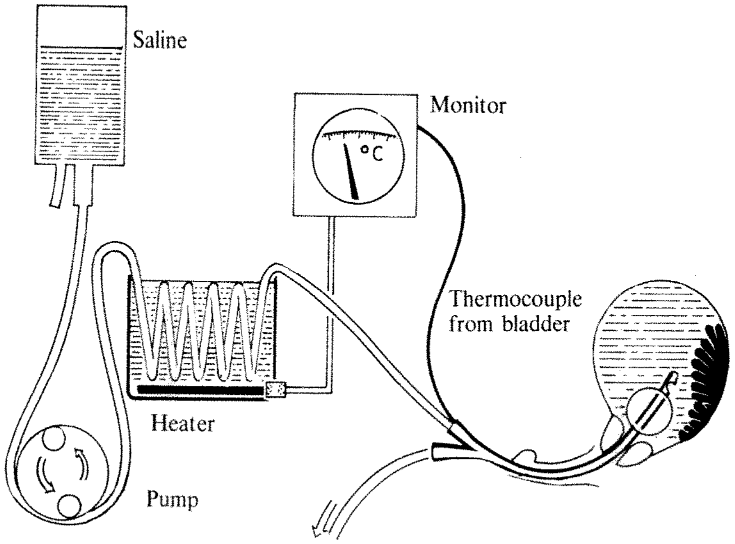

Fig. System for hyperthermic bladder irrigation.

of destroying tumour remaining after previous radiotherapy, because he had refused cystectomy, all the epithelium and tumour was destroyed and the patient's potency was unchanged. Cystoscopic follow-up shows complete loss of tumour in the second.

The highest temperature recorded in the parietal layers of the bladder or within the rectum during the hyperthermic irrigation has been 45°C. No patient had any systemic reaction and discomfort was minimal. Following irrigation a small amount of blood-stained serous fluid was passed from the urethra each day for the first week or two.

One patient developed a burn in the terminal urethra which led to a stricture.

Discussion

The deliberate use of hot saline to destroy the lining of the bladder in patients was at first a concept which we approached with caution and apprehension, so that we began by using a temperature which was too low to do any good. From the results so far obtained in this preliminary study it is clear that in order to get uniform necrosis of the epithelium and the muscle of the bladder, one must use an irrigant which is sufficiently hot, and continue the irrigation for a period of time which is sufficiently long. It is not yet certain what are the correct temperatures or times; lower temperatures of 50° to 60°C were ineffective even up to 2 hours, since they produced only patchy destruction of epithelium and no change in the muscle; a temperature of 80°C with a 5-min exposure time was too short and left islands of epithelium and tumour behind, while the longer period of 10 to 15 min led to consistent destruction of the epithelium and muscle of the bladder and regularly stopped otherwise intractable haemorrhage.

This method is not put forward as a substitute for cystectomy in the usual case for which cystectomy is indicated, nor is it suggested that it is likely to be appropriate for more than a limited group of cases. Nevertheless, it seems to offer great advantages for certain groups of patients. First, where more conservative methods have failed, it appears to be a safer way of controlling haemorrhage than cystectomy. Secondly, when patients refuse cystectomy for one reason or another, irrigation with hot saline may offer a way of destroying their bladder tumour without interfering with potency. Thirdly, it should give good palliation in selected T4 patients and further experience may show that it is of value in treating other infiltrating tumours in poor-risk patients, or those in whom radiotherapy has failed. So far no damage to viscera has occurred, though this is clearly a possible hazard, but the 1 patient who developed the thermal injury to his urethra suggests that this is a possible drawback which might necessitate modification of the system at present in use. Urinary diversion is necessary in every case.

It is suggested that hyperthermia may have a valuable, if limited, role in the urologist's armamentarium.

Summary

Experience with 10 cases of hyperthermic irrigation of the bladder suggests that irrigation with saline at 80°C for 10 to 15 min will stop bleeding and destroy epithelium and muscle layers without causing visceral injury or systemic disturbance.

It may be preferable to cystectomy in certain poor-risk patients, or in those who refuse cystectomy for fear of impotence.

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Urodynamic Findings in Adult Females with Frequency and Dysuria

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Many believe outflow obstruction to be important in the aetiology of "recurrent cystitis" or urethral syndrome. Bladder neck stricture, bladder neck dysfunction, distal urethral stenosis and dyssynergic distal urethral obstruction are terms that appear regularly in a voluminous literature on this subject (Lyon and Smith, 1963; Lyon and Tanagho, 1965; Turner Warwick *et al.* 1973). The results of treatment by urethral dilatation, internal urethrotomy or external meatoplasty have frequently been reported in both young and adult females (Lyon and Smith, 1963; Kerr, Leadbetter and Donahue, 1966; Brannan *et al.*, 1969; McLean and Emmett, 1969; Harvard, 1097; Farrar, Green and Handley Ashken, 1973; Zimskind and Mannes, 1973.) These uncontrolled trials have in common a cure rate of about 70%. The significance of a presumed outflow obstruction has, however, been questioned by the findings of the few prospective trials that have been conducted (Hendry, Stanton and Innes Williams, 1973; Kaplan, Sammons and King, 1973). In these studies results were no better for urethral dilation or internal urethrotomy, than medication alone.

The aim of this study was to define the role of outlet obstruction in these patients presenting with increased frequency and dysuria.

Patients

200 successive referrals of adult females with recurrent dysuria and increased frequency were studied. 30 patients were excluded because they were either unable or unwilling to be admitted for investigation or were still awaiting assessment. 14 patients (7%) were excluded because of IV urogram abnormalities requiring major surgery or other treatment inappropriate in the context of a urinary infection clinic. These were hypernephroma (1), calculi (3), renal tuberculosis (1), pelvi-ureteric junction obstruction (1), duplex with scarring (3), vesico-ureteric reflux (3) and bladder carcinoma (2).

There remained 156 patients who are the subject of this analysis. The age range was 17 to 69 years with a mean of 34 years (Fig. 1).

Methods

All commonly used methods of assessing outflow obstruction have been employed and are classified as symptoms, signs and investigations.

Symptoms. Patients were considered to have obstructive symptoms by giving a history of hesitancy, poor stream and/or a feeling of incomplete emptying, in addition to recurrent increased frequency and dysuria.

Signs. The finding of a large or moderate residual urine on the post-micturition film of an IVU series. Small or dubious residuals were not considered due to the subjective nature of this

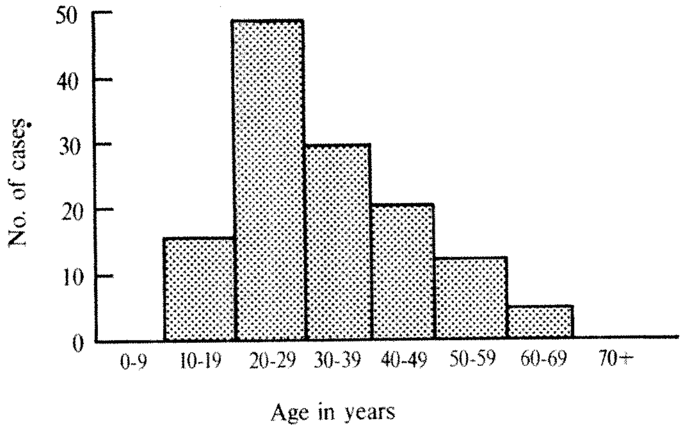

Fig. 1. Age distribution. Mean: 34·7 years ±13. Range: 17 to 69 years.

observation. Urethral calibre was determined prior to cystoscopy under general anaesthesia. Bladder trabeculation was recorded only when unequivocal with the bladder filled to capacity.

Investigations. Residual urine was measured by catheterisation before the urethral pressure profile which was performed by the method of Brown and Wickham (1969) as modified by Harrison and Constable (1970). Cystometry was performed with the patient seated on a modified commode, with a filling rate of 150 ml/min routinely used. Bladder instability was recorded when observed. Values for maximum intrinsic voiding pressure and peak urine flow rate were obtained and from these a calculated urethral resistance was derived using maximum voiding pressure/peak flow rate^2 (Pierce, 1963).

Other Observations. Bacteriuria was established by finding 10^5 organisms/ml in a clean catch or cystoscopy specimen or urine. Urethral and vaginal swabs were examined for monilia, *Trichomonas vaginalis* and corynebacterium (Haemophilus) vaginale. No case of gonorrhoea was found.

Micturating cystography was performed when indicated, for example by a suspicion of reflux. Shopfner (1967) has shown the poor diagnostic value of voiding X-ray studies in conditions such as urethral stenosis. Synchronous video pressure/flow cystography was used only in difficult cases with incontinence and not as a routine. 6 cases of reflux were found, 3 of which required surgery.

Table I

The Relationship between Obstructive Symptoms and Abacteriuria

	Bacteriuria	Abacteriuria	Total
Obstructive symptoms	16	52	68
No obstructive symptoms	40	48	88
Total	56	100	156

$\chi^2 = 8{\cdot}013\ (0{\cdot}025 > P > 0{\cdot}01)$.

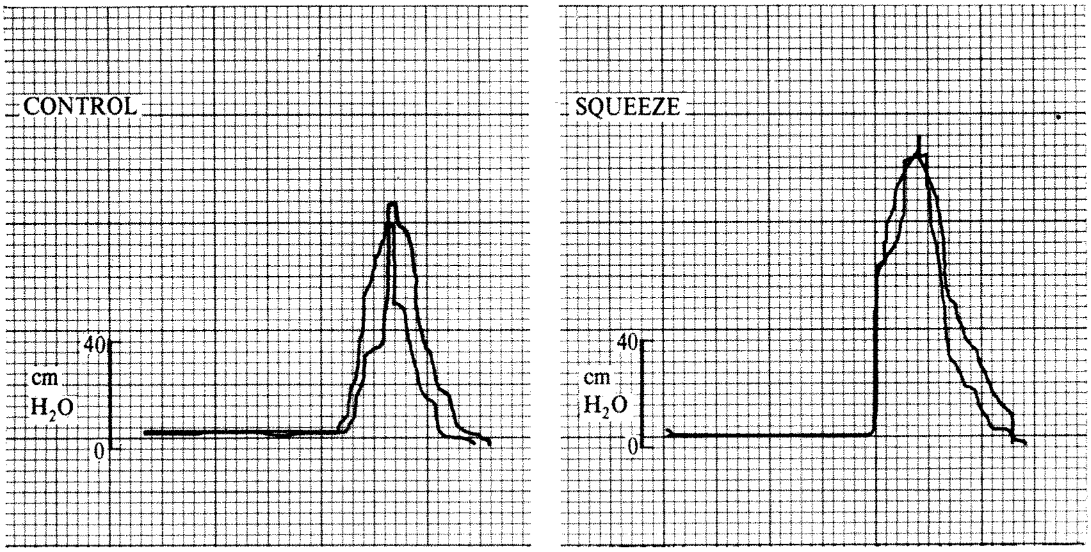

Fig. 2. Urethral pressure profile. Typical traces at rest and with voluntary perineal squeeze.

Results and Discussion

The data obtained were analysed for correlations between the various indices of outflow obstruction that were recorded.

Obstructive Symptoms. 68 patients (44%) complained of difficulty with voiding or poor stream. Measures of outflow obstruction in this group were not significantly different from those of the whole. These symptoms are not a guide in assessing potential outflow obstruction. Obstructive symptoms were more common in abacteriuric than bacteriuric patients (Table I).

Residual Urine on IVU. 3 patients were considered to have significant residuals on the post-micturition film of an IVU series. However, when the residual urines of these patients were subsequently measured by catheterisation they were found to be 5, 10 and 225 ml. This small group was not further analysed.

Measured Residual Urine. 104 patients (67%) had a measurable residual urine with a range of 1 to 225 ml (mean 22·7 ml ± 40·6). There were neither statistically significant mean differences nor correlations between the measured residual urine and any other parameters of outflow obstruction. There was no association between residual urine and bacteriuria.

Urethral Pressure Profile. The mean value of the resting urethral pressure for the whole group was 74·5 cm $H_2O \pm 24{\cdot}6$ (Range 15 to 140). In addition to resting pressure, values for urethral pressure with voluntary perineal squeeze were recorded (Fig. 2). These values and age-corrected (pressure + age) values were analysed, as Harrison (1971), Edwards and Malvern (1974) had found a significant negative age correlation. This analysis, however, showed only a poor negative correlation with age ($r = -0{\cdot}23$) and that urethral pressure rose in the 2nd, 3rd and 4th decades (Fig. 3). The squeeze difference tended to be lower in the middle decades possibly because of increasing parity. The only correlation found in this part of the analysis was a negative one between profile height and calibration ($r = -0{\cdot}207$). This was barely statistically significant,

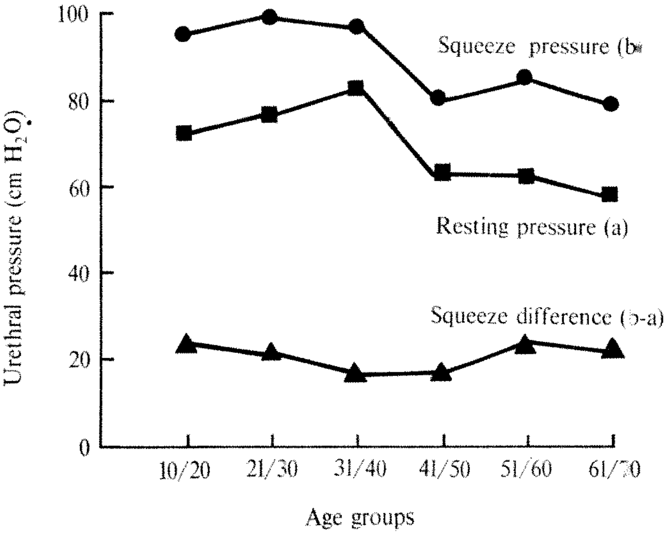

Fig. 3. Urethral pressure and age; (a) resting pressure; (b) pressure with voluntary perineal squeeze and (b-a) squeeze difference. For resting pressure and age, $r = -0{\cdot}23$ ($0{\cdot}01 > P > 0{\cdot}002$).

($0{\cdot}05 > P > 0{\cdot}02$). Here, there is a significant trend but one without individual predictive value in the clinical situation. Many of the correlation coefficients approached zero indicating almost random distribution (Table II).

The mean resting urethral pressure was found to be lower in patients with bacteriuria than those without (Table V). This supports the observations of Mayo and Hinman (1973) that the mid-urethral high-pressure zone is an important barrier to bacterial ascent. A lower resting pressure in the presence of *Trichomonas vaginalis* vaginal infection ($P < 0{\cdot}01$) was also found.

Voiding Pressure/Urine Flow Studies. These measurements, being related to the dynamic aspects of micturition, might be expected to provide a truer picture of urethral function. However, there were no correlations with other indices of outflow obstruction. The mean calculated urethral resistance in this series was 0·24 ± 0·46. Claridge and Shuttleworth (1964) found a mean value of 0·4 in normal subjects with a range of 0·2 to 97·5 in obstructed cases. Smith (1968) defined

Table II

Correlation Coefficients of Urethral Pressure with other Measures of Outflow Obstruction

	Correlation coefficient	Significance
Resting pressure and calibration	−0·207	$0{\cdot}05 > P > 0{\cdot}02$
Resting pressure and residual	−0·04	$P > 0{\cdot}2$
Resting pressure and urethral resistance	−0·0005	$P > 0{\cdot}2$
Age-corrected resting pressure and calibration	−0·715	$P > 0{\cdot}2$
Squeeze pressure and urethral resistance	−0·037	$P > 0{\cdot}2$
Age-corrected squeeze pressure and peak flow rate	−0·067	$P > 0{\cdot}2$

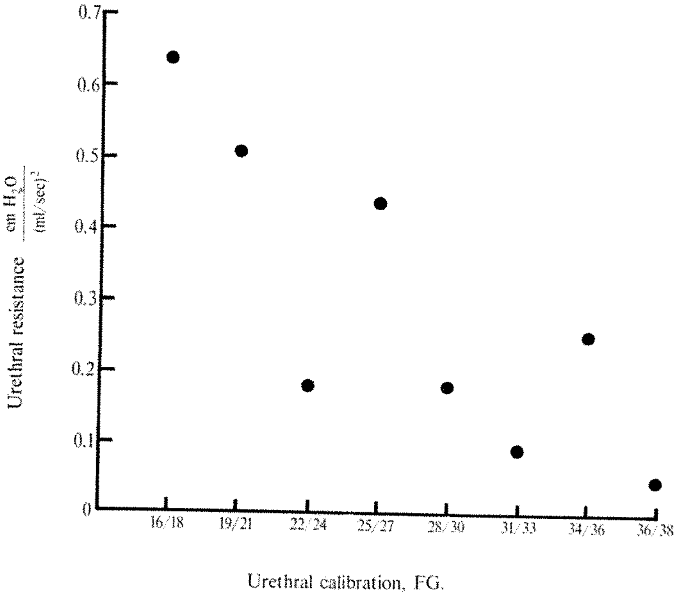

Fig. 4. Mean urethral resistance for successive increments of urethral calibration, $r = -0{\cdot}27$ ($0{\cdot}01 > P > 0{\cdot}002$).

the upper limit of normal as 0·3. Comparison of urethral resistance with other measures of outflow obstruction was unrewarding apart from a significant correlation with calibration (Table III). Again, although a significant trend has been revealed there is poor individual predictive value. This is shown in Fig. 4, in which the scatter of results has been reduced by plotting mean values of urethral resistance for successive groups of increments of calibration.

Urethral Calibration. The mean for all patients was 25FG ± 6 (Range 14 to 38). The degree of correlation between calibration and urethral resistance and also between calibration and resting urethral pressure has already been noted. No other correlation has been found in comparing calibration with other measures of outflow obstruction (Tables II and III).

Trabeculation. Only 23 (15%) were considered to have unequivocal trabeculation with the bladder filled to capacity. In no case was there a correlation between trabeculation and any of the indices

Table III

Correlation Coefficients of Pressure/Flow Studies with other Measures of Outflow Obstruction

	Correlation coefficient	Significance
Max. voiding pressure and calibration	−0·008	P > 0·2
Max. voiding pressure and urethral pressure	+0·116	P > 0·2
Peak flow rate and calibration	+0·123	P > 0·2
Peak flow rate and residual	−0·092	P > 0·2
Urethral resistance and calibration	−0·270	0·01 > P > 0·002
Urethral resistance and urethral pressure	−0·0005	P > 0·2
Urethral resistance and residual urine	−0·034	P > 0·2

Table IV

The Relationship between Trabeculation and Bladder Instability

	Stable bladder	Unstable	Total
Trabeculation	10	13	23
No trabeculation	103	30	133
Total	113	43	156

$\chi^2 = 11{\cdot}36$ ($P < 0{\cdot}005$).

of outflow obstruction. There was, however, a strong association between trabeculation and bladder instability (Table IV).

Bladder Instability. Bladder instability (as defined by uninhibited systolic detrusor contractions) was found in 43 (27·5%) of patients. This is a high percentage compared with other studies. Lapides and Costello (1969)—17%, Webster (1975)—4%. This may be due to a degree of preselection of the patients in this series since a number of them have been referrals from elsewhere. Referrals often represent treatment failures, possibly because in these cases bladder instability was not recognised as the cause of their presenting symptoms. The detection of bladder instability is important as these patients are likely to respond to anticholinergic drugs, if given in adequate doses. Apart from the association with trabeculation no correlations could be found between bladder instability and any of the various indices of outflow obstruction. The mean age of those with instability was lower (31·38 years ± 12·03), than those without but not at a statistically significant level ($0{\cdot}1 > P > 0{\cdot}5$).

Other Observations. Bacteriuria was found in 56 (36%) of patients. This is lower than the usually reported figure of 45%. Almost all patients had had 1 or more courses of antibiotics prior to referral. The association between abacteriuria and obstructive symptoms has already been noted (Table I). The only other significant finding was that bacteriuria was twice as common in patients with vaginal infection (Table V). No other significant correlations were found in the analysis of vaginal infection, cervical erosian and bladder capacity.

It could be argued that by trying to obtain correlations using the full range of results in a group of patients such as this, important correlations might be missed at the extremes of the range. Therefore an attempt has been made to define a group of patients with outflow obstruction by repeating the analysis using only those with a low urethral calibre, high resting urethral pressure, high bladder voiding pressure, low peak flow rate or high calculated urethral resistance, in turn. The only significant finding was of a reduced urethral calibre in patients with a peak flow rate of less than 10 ml/sec ($0{\cdot}025 > P > 0{\cdot}01$). These patients, 8% of the total (12 in number), may represent a group with outflow obstruction. No other significant correlations were found.

Conclusions

In adult women with recurrent increased frequency and dysuria, whether bacteriuric or abacteriuric, it has not been possible to define convincingly a group with outflow obstruction. At most, 8% may have outflow obstruction but the remaining 92% almost certainly do not, unless present methods of assessment are inadequately sensitive to detect them.

Table V

	Bacteriuric	Abacteriuric	Total
Vaginal infection	24	21	45
No vaginal infection	32	79	111
Total	56	100	156

$\chi^2 = 8{\cdot}35\ (0{\cdot}025 > P > 0{\cdot}01)$

Resting Urethral Pressure:

Abacteriurics $76{\cdot}71 \pm 24{\cdot}29$ cm H_2O
Bacteriurics $67{\cdot}87 \pm 22{\cdot}36$ cm H_2O $(0{\cdot}5 > P > 0{\cdot}02)$.

The role of urethral dilatation or internal urethrotomy in these patients is doubtful. Moreover, in the evaluation of these forms of treatment, the use of the indices of obstruction that have been assessed in this analysis would yield results of dubious value.

27% of patients had bladder instability. Trabeculation was associated with bladder instability rather than with outflow obstruction.

There is a worthwhile return from IV urography in these patients. 7% had major abnormalities.

Summary

Urodynamic findings, and in particular measures of outflow obstruction in a consecutive series of 156 women presenting with recurrent increased frequency and dysuria, have been analysed.

Poor correlation between these various measures has been demonstrated; at most only 8% of these patients have demonstrable outflow obstruction. More than a quarter of the patients had bladder instability.

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The Painful Prostate

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Patients presenting with irritative micturition symptoms, perigenital pain and sexual dysfunction continue to present a major management problem. The usual diagnosis made on purely clinical grounds is that of chronic prostatitis but positive laboratory evidence of infection has been obtained to a varying degree (Meares and Stamey, 1972; Lennert, Mondorf and Dathe, 1967; Mardhe and Colleen, 1975). Attempts to confirm the diagnosis histologically have also met with varying success (Schmidt and Patterson, 1966; Neilson and Christensen, 1972; Smart and Jenkins, 1973). Urological histopathologists conclude that a diagnosis of chronic prostatitis can only be made on clinical grounds (Cameron, 1974).

A study of adult males with the symptoms and signs of "chronic prostatitis" has been undertaken to establish the incidence of infective, autoimmune, psychological and urological disorders in this relatively common clinical disorder.

Patients and Methods

An in-patient study was carried out on 105 adult males with the symptoms and signs of "chronic prostatitis" present for a minimum of 6 months. The clinical and laboratory findings and the results of follow-up for up to 3 years are presented.

Urological Investigations

A detailed history and physical examination were obtained from each patient. A full blood count, E.S.R. urea, electrolytes, W.R., 3 early morning specimens of urine for acid-fast bacilli, chest X-ray, intravenous urogram and urine flow rate were carried out.

Stamey Localisation Studies

Urinary tract localisation studies were carried out according to the technique described by Meares and Stamey (1972). The first voided specimen of the morning was used and collection was supervised at all stages. The first 5 ml of urine (VB1) and a mid-stream urine (VB2) were obtained, then prostatic massage performed and the prostatic secretions (EPS) collected. When possible the next voided 5 ml of urine (VB3) were collected, this being of particular importance in patients from whom EPS was not obtained. The 4 specimens thus collected were each divided into 3, 1 for pus cell counting in a Fuchs-Rosenthal counting chamber, 1 for semi-quantitative bacterial culture using blood agar and MacConkey's media and the 3rd for virus and chlamydia culture.

Psychological Assessment

This was carried out by questionnaire (Goldberg, 1972) using the Eysenck Personality Inventory and the General Health Questionnaire. Patients with chronic prostatitis have been compared with 22 age-matched males admitted for minor non-urological surgery.

Auto-antibody Studies

Serological autoimmune profiles using a standard immunofluorescent technique were performed and compared with the age-matched controls and with sera from 235 subjects attending local blood donor sessions.

Table I

Diagnosis in 105 Adult Males presenting with Symptoms and Signs of Chronic Prostatitis

Chronic bacterial prostatitis		51
Staph. albus	27	
Pathogens	24	
No abnormality found		27
Other urological pathology		27
Chronic cystitis		
Transitional cell carcinoma bladder	2	
Outflow tract obstruction (on endoscopy)	12	
Low urine flow rate (normal endoscopy)	5	
Urethral stricture (unsuspected)	5	
Diverticular disease	1	
Diabetic bladder	1	
Neurogenic bladder	1	

Table II

"Chronic Prostatitis": Age and Duration of Symptoms

	Number in group	Mean age (yrs)	Mean duration of symptoms (yrs)
Chronic bacterial prostatitis			
Pathogenesis	24	56	4·5
Staph. albus	27	48·5	5
Other pathology	27	51·5	4·3
No abnormality found	27	38	4·5
Controls	22	50	...

Endoscopic Assessment

Cysto-urethroscopy was performed under general anaesthetic. The appearances of the urethra, prostate, bladder neck and bladder were recorded. Following this assessment and depending upon available data and the patient's wishes, either a transrectal prostatic biopsy or a transurethral prostatectomy were performed. The type of biopsy was the aspiration technique using a Franzen needle in 14 patients, with cytological examination of the aspirated material and a core of tissue obtained with the Trucut needle in 46 patients for histological examination. No biopsy was obtained in 3 patients. All cases were given antibiotic cover for 5 days, this being continued for 6 weeks if the bacteriology results suggested an infective aetiology. Transurethral prostatectomy was performed eventually on 49 patients, the procedure being carried out twice in 7 cases. Every attempt was made to resect all the prostatic tissue proximal to Nesbit's fold; frequent rectal examination was required to allow this to be achieved with safety. The prostatic chips and the small calculi that were frequently encountered were collected in a sterile sieve. Prostatic chips from the various levels of the prostate and the calculi were sent immediately for bacteriology, being inoculated into a Robertson's cooked meat broth medium and incubated for 24 hours. Other prostatic samples from various levels were snap-frozen in liquid nitrogen and stored. The remainder was examined by standard histological techniques.

Treatment

Definite urological disorders were treated appropriately. Patients in whom bacteria were localised to the EPS were treated with antibiotics according to sensitivities for 6 weeks and then reviewed. If there was no improvement after this course of antibiotics a transurethral prostatectomy was suggested to those patients in whom sterility was not a problem Patients with bacteria localised to the EPS and with evidence of outflow obstruction were offered transurethral prostatectomy on the same basis Finally, in patients in whom no abnormality was found, strong reassurance was given and transurethral prostatectomy undertaken only in patients with severe, persistent symptoms.

Follow-up

All patients were reviewed at 6 weeks, 3 months, 18 months and up to 3 years in some cases. Late reviews were carried out using a postal questionnaire.

Results

It is possible to divide the patients into 2 groups from the Stamey localisation studies and the culture of the resected prostate when available. In 51 cases bacteria were localised to the expressed prostatic secretions (EPS) or were present in the prostatic tissue. This group can be subdivided into those with well recognised urinary pathogens (24) and those with *Staphylococcus albus* (27). The remaining 54 patients may also be subdivided into those with a distinct urological abnormality (27) (Table I) and those in whom all investigations have proved negative (27). In analysing the results of the survey the 4 sub-groups have been compared with each other and where appropriate with a group of 22 age-matched males with minor non-urological surgical problems.

Clinical Findings

The mean age of each group is shown in Table II and it may be noted that the group with no detectable abnormality are significantly younger than the other patients. There was no difference in duration of symptoms between the groups. Comparison of the incidence of the individual symptoms in the 4 groups shows that irritative micturition symptoms, haematuria, restricted flow and normal sexual activity are less common in the group with negative findings but these differences are small (Fig. 1). A past history of venereal disease was also more commonly associated with negative findings (Fig. 2) Severe prostatic tenderness was equally common in all 4 symptomatic groups (78 to 92%) but less frequent in the controls (25%).

Significant urographic changes were seen in 11 patients. Ureteric dilatation was noted in 5 cases and was bilateral in 4. Of these patients 1 had tuberculous prostatitis, 1 eventually developed carcinoma of the bladder and the other 3 had outflow obstruction as assessed by flow measurement only. Of the remaining 6 with abnormal urograms, 3 had small renal calculi, 2 had bladder diverticula and 1 had a partial duplex system with a calyceal diverticulum. In 6 other patients prostatic calcification was noted.

Psychological Assessment

The 2 questionnaires used in this study provided numerical values for the degrees of neuroticism of the patient, the higher the score the greater the degree of neurotic tendency. For the purpose of this paper patients with high scores on both questionnaires have been labelled neurotic (11 for the General Health Questionnaire and 14 for the Eysenck Personality Inventory). Only the group with no detectable abnormality was significantly more neurotic than the other groups or the controls ($P > 0{\cdot}01$).

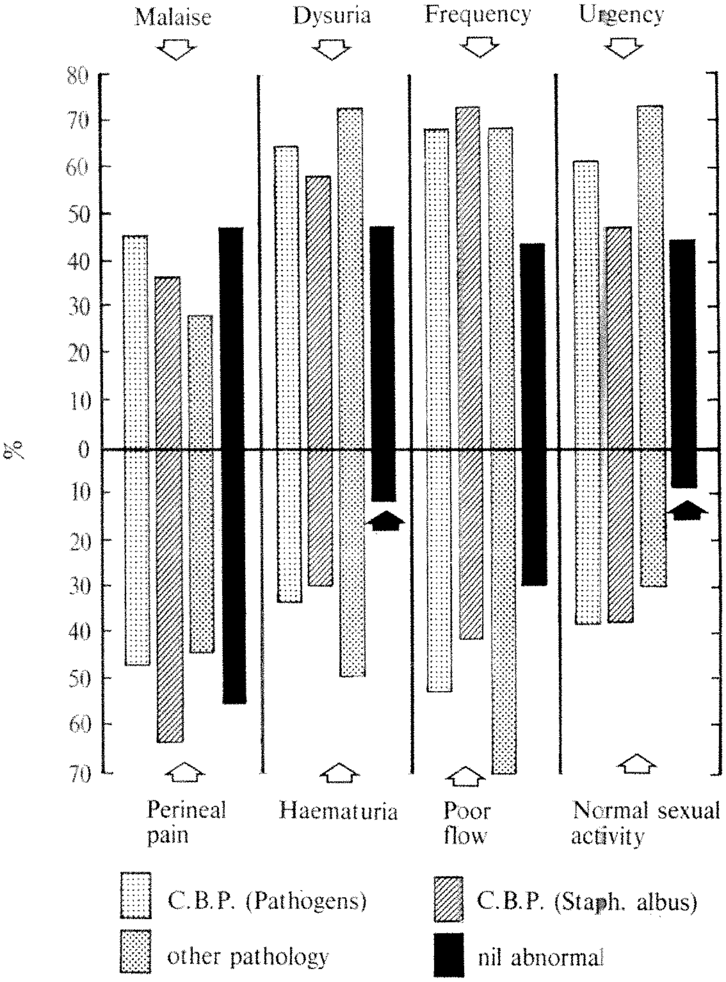

Fig. 1. Comparative incidence of symptoms and signs.

Auto-antibody Studies

The results of tests for organ-specific antibodies and non-organ-specific antibodies showed no difference between the various groups and the age-matched controls, or the random panel of blood donors with the exception of the antibody to gammaglobulin. The incidence of this antibody was significantly higher in the symptomatic patients taken together than in blood donors ($P < 0{\cdot}001$) but was not significantly different from the incidence in age-matched controls.

Flow Rates and Endoscopy

In 59 patients both flow rate and endoscopy were normal. In 18 endoscopy was normal but flow rates were poor and in the remaining 28 patients flow and endoscopy were abnormal (Table IV). Bladder biopsies were taken with the resectoscope in all patients with the appearances of chronic cystitis. In 2 patients after intervals of 12 and 18 months, during which time several further bladder biopsies were taken, transitional cell carcinoma of the bladder appeared.

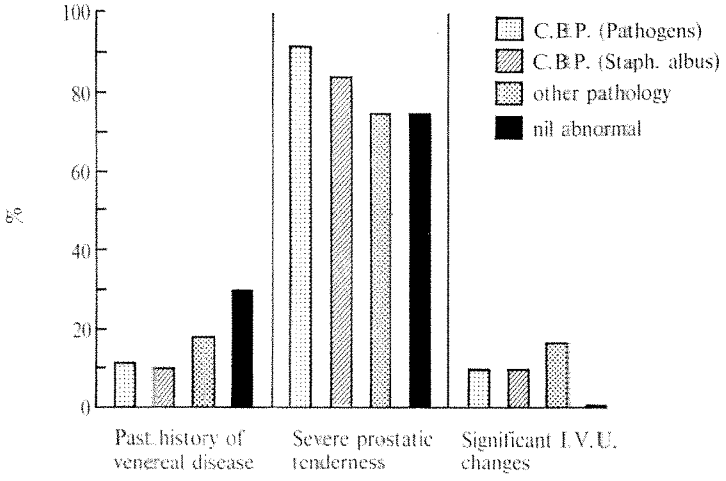

Fig. 2. Relationship between clinical findings and incidence of "chronic prostatitis".

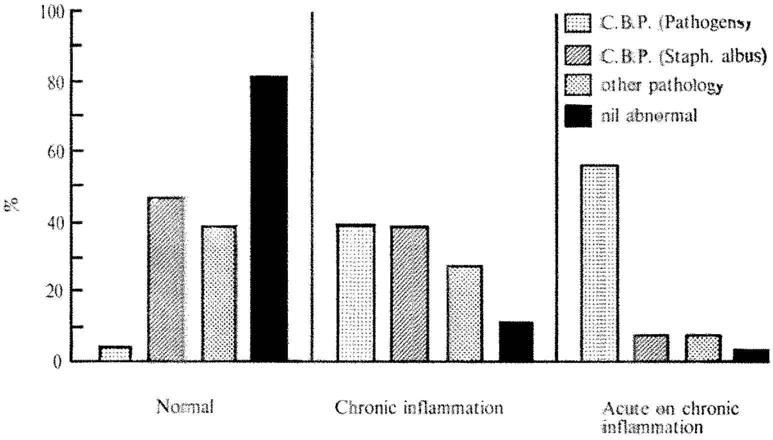

Fig. 3. Comparative incidence of prostatic histology.

Prostatic Bacteriology and Histology

The value of prostatic tissue culture is illustrated by the finding of 8 patients with negative localisation studies but positive prostatic bacteriology, 5 pathogenic and 3 *Staphylococcus albus* (Table III). The 9 patients with bacteria localised to the EPS but negative prostatic culture were mainly *Staphylococcus albus* (7) and the majority (6) had received a 6-week course of antibiotics prior to prostatectomy.

The prostatic biopsies and resected prostatic tissue have been examined histologically for evidence of benign hyperplasia, malignancy and inflammatory changes (Fig. 3). A light chronic inflammatory cell infiltrate has been classified as normal. All but 1 of the patients with pathogenic bacteria localised to the prostate had significant inflammatory changes and in over half, this was acute on chronic in type. Significant inflammatory changes were seen in approximately half of the other pathology and the *Staphylococcus albus* groups but acute on chronic change was infrequent. Of the group with negative findings on EPS, 21 out of 27 had normal histology.

Table III

Comparison of the bacteriological culture of expressed secretion and prostatic tissue in 49 patients

	Expressed prostatic secretion culture	
	Positive	Negative
Prostatic tissue culture		
Positive	11	8
Negative	9	21

Table IV

"Chronic Prostatitis": Results of endoscopy and flow measurements

	Endoscopy and flow normal	Endoscopy normal flow rate decreased	Endoscopic evidence of outflow obstruction, flow rate decreased
Chronic bacterial prostatitis			
Pathogens	12	6	6
Staph. albus	15	7	5
Other pathology	5	5	17
No abnormality found	27	...	...

Results of Follow-up

The fate of the 105 patients in this series has been studied at 18 months to 3 years. 3 patients have died of unrelated disorders at 6, 12 and 12 months. Transurethral prostatectomy was carried out on 16 patients with pathogenic bacterial prostatitis, 12 with staphylococcus albus prostatitis, 15 with other urological disorders and 6 with negative findings. Comparison of the 4 sub-groups shows that three-quarters of each group have improved but more of the patients in the pathogenic bacterial prostatitis group are asymptomatic (Fig. 4).

Discussion

The results of this survey illustrate the need for full evaluation of all patients with the symptoms and signs of chronic prostatitis, however neurotic the patient may appear. Carcinoma of the bladder, urethral stricture, prostatic obstruction, pericolic abscess, bladder neuropathy, diabetes mellitus, radiolucent bladder calculi and "dyskinesia" (Turner-Warwick *et al.*, 1973) of the bladder neck can all mimic chronic bacterial prostatitis. From the purely clinical point of view it is not possible to separate the various aetiologies, although the groups with negative findings may be distinguished to a certain degree by their lower age and lack of satisfactory sex lives.

The incidence of chronic bacterial prostatitis (48·5%) in this study is higher than in the most recent published series (Fritjofsson, Kihl and Danielsson, 1974; Mardh and Colleen, 1975)

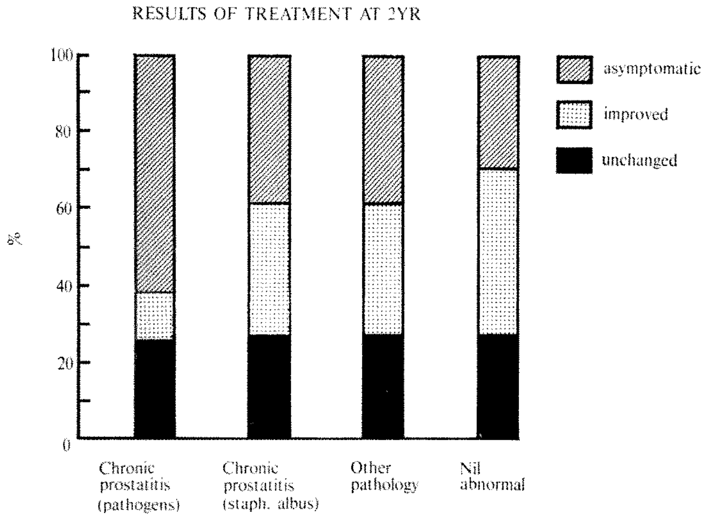

Fig. 4. Results and treatment at 2 years.

although this is probably accounted for by the additional data obtained from prostatic tissue culture and a difference in case selection. By including staphylococcus albus as a pathogenic organism Drach (1974) has found an incidence of 40% chronic bacterial prostatitis in a similar group of patients. The same author has also noted the value of transurethral prostatic biopsy as a means of confirming the presence of bacteria in the prostate and was able at endoscopy to find a number of unsuspected lesions (42%) including 7 cases of urethral stricture.

Lennert, Mondorf and Dathe (1967) made a psychological diagnosis by exclusion in a number of patients but the results are clearly dependent on the depth of the urological investigation and the length of follow-up. No prospective psychological assessment was carried out and prospective studies are lacking in the literature.

In the results presented here the patients with detectable abnormalities and the controls had a similar level of neuroticism which was significantly less than the patients with negative findings. This therefore suggests a psychological basis for 25% of the cases in this study, a much lower figure than that of 49% suggested by Lennert *et al.* (1967). Of practical importance is the observation that the patients who are symptomatic at 18 months to 3 years are significantly more neurotic (60%) than those who are asymptomatic (20%). We would suggest that some form of objective psychological screening be carried out before surgery is embarked upon.

In this study we have failed to show any significant difference in the incidence of organ-specific or non-organ-specific autoantibodies in any of the symptomatic groups when compared with controls. With the exception of an increased incidence of antibody to gammaglobulin, similar results were obtained on comparison with a random panel of blood donors. The concept that chronic prostatitis has an autoimmune aetiology seems unlikely in view of the fact that the majority of autoimmune disorders show a marked degree of serological overlap and a tendency for more than one autoimmune disorder to occur in the same individual (Roitt, 1971). It is also claimed (Wright, 1975) that the presence of smooth muscle antibodies and A.N.A. can be considered markers of an autoimmune condition. We have been unable to show any significant difference in the incidence of these antibodies in patients with chronic prostatitis when compared with either controls or blood donor groups.

A significant degree of prostatic inflammatory change was seen in 95% of patients with pathogenic bacteria localised to the prostate and this was acute on chronic in over half the cases

This compares with only 15% significant inflammation in the prostates of patients with completely negative findings. Thus, although a diagnosis of chronic prostatitis may not be made on histological grounds, examination of prostatic tissue histologically, appears to support the view that chronic bacterial prostatitis is an infective process within the prostate gland. The histological findings in the *Staphylococcus albus* group showed a low-grade form inflammation in approximately half of the cases. Benign hyperplasia of the prostate was seen most frequently in the pathogenic group (33%) and least often in the negative findings group (8%). This may account for some of the differences in degree of prostatic inflammation (Cameron, 1974) in the 4 groups but by no means all.

Treatment has been most successful in the pathogenic prostatitis group (52% asymptomatic) and as one might expect least successful in the negative findings group (28% asymptomatic). Approximately 25% of each group remains unchanged and the others have shown variable degrees of improvement. There are no other prospective studies available for comparison but the above results are similar to those to be anticipated from the literature (Alyea, 1970). The results of transurethral prostatectomy are better than conservative measures but the differences are small. However, it should be remembered that the patients treated by surgery were, in the main, those with more severe symptoms. The early results of transurethral resection for clinical chronic prostatitis were comparable with those for benign hyperplasia (Smart and Jenkins, 1973). These excellent results have not been maintained over 18 months to 3 years but a procedure which results in 50% asymptomatic and 30% improved patients compared with 43% and 22% for conservative measures must be given serious consideration in the resistant case. Numbers are too small to analyse the results of treatment of bacterial prostatitis, with and without outflow obstruction, with any statistical certainty. However, from the figures available the presence of outflow obstruction appears to influence favourably the outcome of transurethral resection where bacteria have been localised to the prostate.

Conclusions

The results of this study suggest that full urological assessment is required in all patients with clinical chronic prostatitis. This should include Stamey localisation studies, flow rate measurement and endoscopy. Transurethral prostatic biopsy for bacteriology and histology will be of value in the equivocal case.

If all these investigations are negative and symptoms persist despite strong reassurance then the patient should be referred for psychiatric assessment and treatment.

Summary

A clinical diagnosis of chronic prostatitis was made on 105 adult males who were subsequently admitted and investigated by Stamey localisation techniques, psychological questionnaires, urine flow studies, cysto-urethroscopy and prostatic biopsy or transurethral prostatectomy.

From the Stamey localisation studies and cultures of the tissue obtained at transurethral prostatectomy a diagnosis of bacterial prostatitis was made in 50%, of which half were *Staphylococcus albus* and half were well recognised urinary pathogens.

Other significant pathology was found in 25% and, particularly of note, were 2 patients who presented with chronic cystitis (biopsy negative) and subsequently developed carcinoma of the bladder. Also in this group were 5 unsuspected strictures and 5 patients with poor flow rates but normal endoscopy.

Investigations in the remaining 25% were all negative except for a significantly higher incidence of neuroticism when compared with the other groups and controls.

Follow-up over 18 months to 3 years shows that treatment results in improvement in 75%. Half of the patients with pathogenic bacterial prostatitis were asymptomatic compared with only a quarter of the group with negative findings. Transurethral prostatectomy is of particular value in patients with chronic bacterial prostatitis and evidence of outflow obstruction. Preoperative psychological screening is helpful in selecting patients suitable for surgery.

We wish to thank Dr J. Guthrie, Dr C. Godber and Mr E. Cuthbert for their assistance with this study. We are also grateful to Mr Bartholomew, Miss Wadsworth and Mrs K. Grantham for preparing the illustrations and manuscript.

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The Ultrastructure of Human Male Urethral Stricture

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All urologists recognise at least 2 kinds of urethral stricture when attempting to dilate them with a bougie. In the past these have been called "soft" and "hard" strictures: the soft or rubbery strictures usually stretch with ease, only to recur within a short time as bad as before; the hard or fibrous strictures "give" with a distinct sensation of overcoming resistance and then remain dilated for a longer period before needing bouginage again. This well recognised difference in the feel of the stricture on the instrument led Hunter, among others, to suggest that one form was caused by spasm and the other by scar. Many and detailed studies of the histology of urethral strictures have been carried out since Hunter's day, nevertheless the aetiology and pathogenesis of urethral stricture is still poorly understood, in spite of the renewal of interest in the condition which has followed the more widespread use of various forms of urethroplasty. At the same time the fundamental problem of fibrosis, which is so important in so many diseases, has become the object of much research, in which former ideas have had to be revised.

The classical description of the histopathology of urethral stricture, based on light microscopy, has been one of fibrous replacement of the corpus spongiosum, with a focal infiltration of chronic and acute inflammatory cells, and scanty fibroblasts (Fig. 1). No special features were ever noted in this scar tissue which would explain the well known clinical differences between the "hard" and the "soft" stricture. The operation of urethroplasty permitted us to obtain fresh tissue from the strictured and the adjacent urethra and to apply newer histological techniques which were capable of giving better resolution than was possible with the light microscope. Unfortunately it was at first difficult to interpret some of our findings, since we had no comparable fresh normal human urethra to compare with the diseased tissue and this led us to study the ultrastructure of the urethra in the baboon and the guinea-pig (Scott and Singh, 1975).

Materials and Methods

Biopsies were obtained at the time of urethroplasty from 20 male patients, in 8 the stricture developed after an inflammatory urethritis, usually gonorrhoea; in 5 the stricture followed trauma; in 3 the stricture followed earlier attempts to repair a hypospadias and in 3 men there was a peculiar short stricture, involving the bulbar urethra which has a number of characteristics which make us believe that it may be of congenital origin (Blandy and Singh, 1975).

Full thickness biopsies were obtained to include the urethral lining. The fresh tissue was divided into 2 to 3 mm cubes and immersed immediately into a solution of 4% paraformaldehyde in Millonig's buffer (Glauert, 1967) for 1 hour and then transferred for a further hour into a solution of osmium tetraoxide in Millonig's buffer. After this period of fixation, blocks were dehydrated through a graded series of alcohols, cleared in propylene oxide and embedded in epoxy resin. Sections 1 micron thick were cut on a Cambridge-Huxley ultramicrotome and stained with 1% toluidine blue. Thin sections were also cut at 700Å, stained with uranyl acetate and lead citrate and examined in a Siemen's Elmiskop IIa Electron microscope.

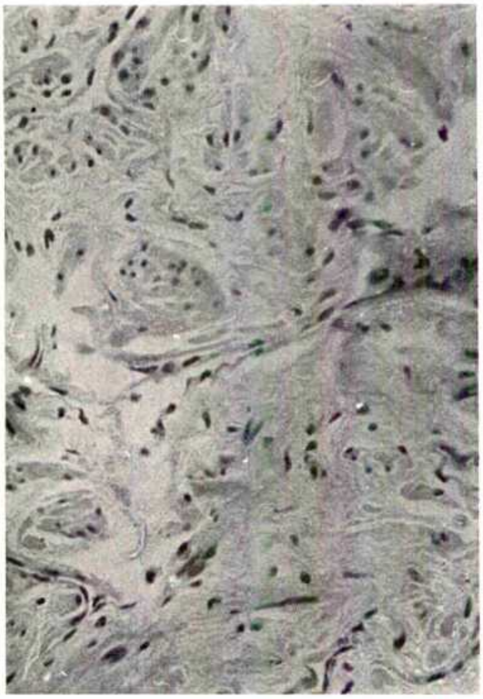

Fig. 1. A light photomicrograph of bulbar urethral stricture showing dense fibrous tissue with infiltration of acute and chronic inflammatory cells. H & E. ×250.

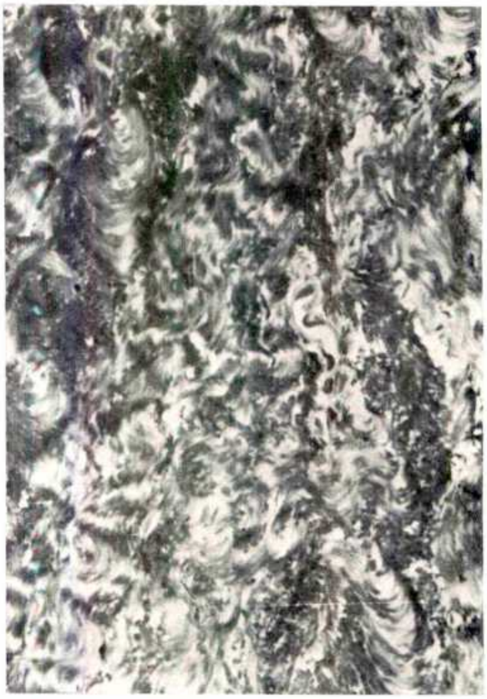

Fig. 2. A light photomicrograph of 1 μm section of post-traumatic stricture tissue showing densely packed collagen and no cells. ×300.

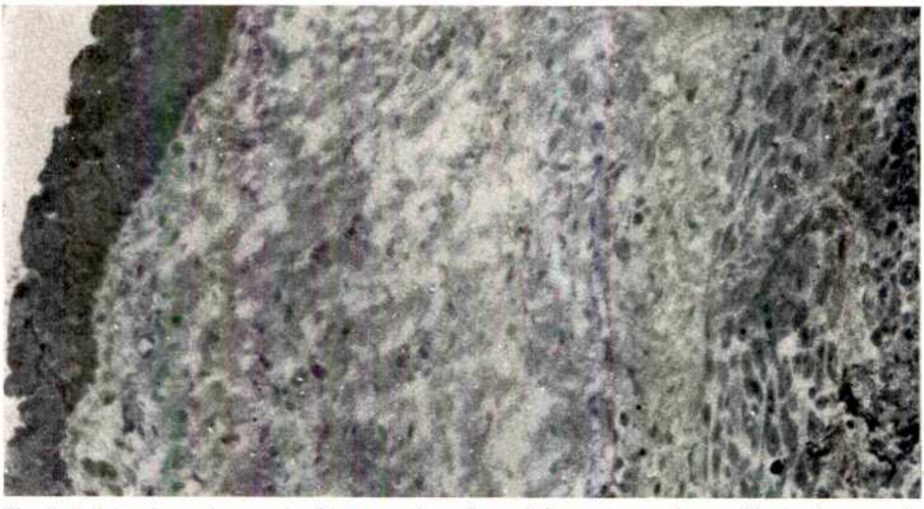

Fig. 3. A light photomicrograph of 1 μm section of post-inflammatory stricture. The lamina propria is wide and packed with dense collagen fibres and demonstrating smooth muscle in the deeper parts. There are no cavernous blood spaces. ×170.

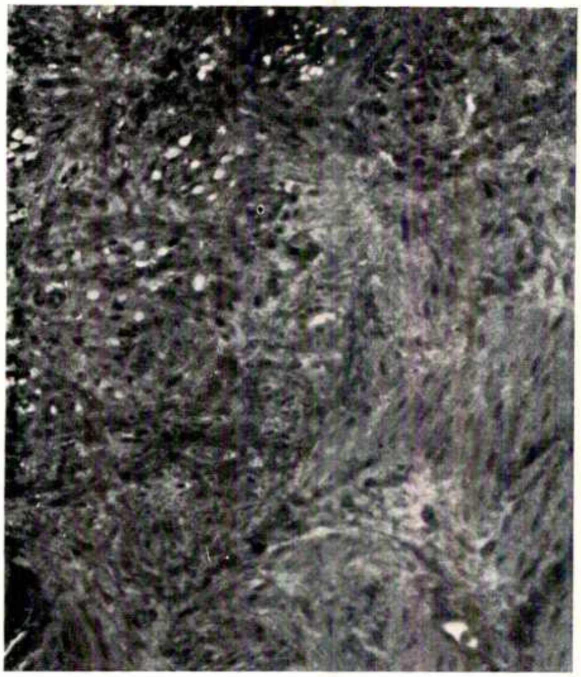

Fig. 4. A light photomicrograph of a 1 μm section of post-inflammatory bulbar stricture demonstrating proliferating smooth muscle in a mass of collagen fibres. × 170.

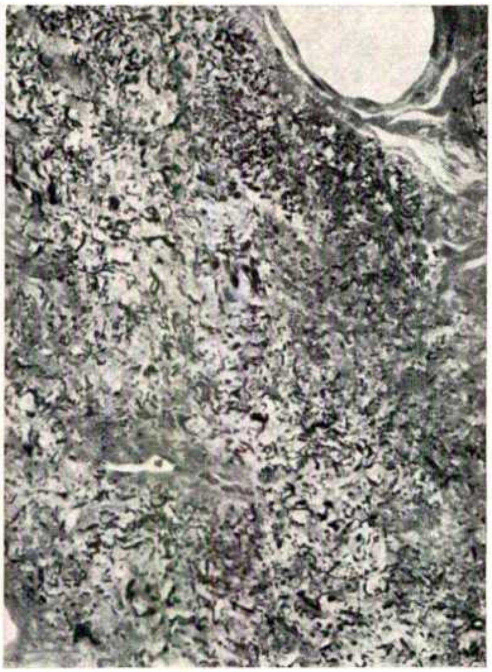

Fig. 5. A light photomicrograph of 1 μm section of post-inflammatory stricture demonstrating the density of elastic fibres—showing as dots or fibres. Collagen fibres can also be seen. × 170.

Results

Urethral Lining

We found a wide variation in the character of the urethral lining: in some cases, especially where the stricture had followed complete rupture of the urethra, it was difficult to recognise any epithelium at all. In most cases the epithelium was stratified squamous and as a rule this was keratinised. Only occasionally did we find the pseudocolumnar stratified epithelium which is the normal lining of the male urethra. The most interesting features of these strictures were found not in the epithelial lining, but in the lamina propria and the corpus spongiosum. They were different in the three kinds of stricture which were examined.

(*a*) *Post Traumatic Membranous Urethral Strictures*

In all 5 biopsies we found dense collagenous tissue in the stricture and a marked paucity of cells (Fig. 2).

(*b*) *Post Inflammatory Strictures*

In all 8 examples we found the lamina propria to be much wider and more fibrous than the normal. The cavernous blood spaces were largely occluded and there were few, if any, fibroblasts or other fibrogenic cells to be seen (Fig. 3). The tissue farther away from the lumen contained varying amounts of collagen and elastic fibres surrounding tissue which resembled smooth muscle cells. These smooth muscle cells were either disposed as bundles or showed an intense proliferation (Fig. 4).

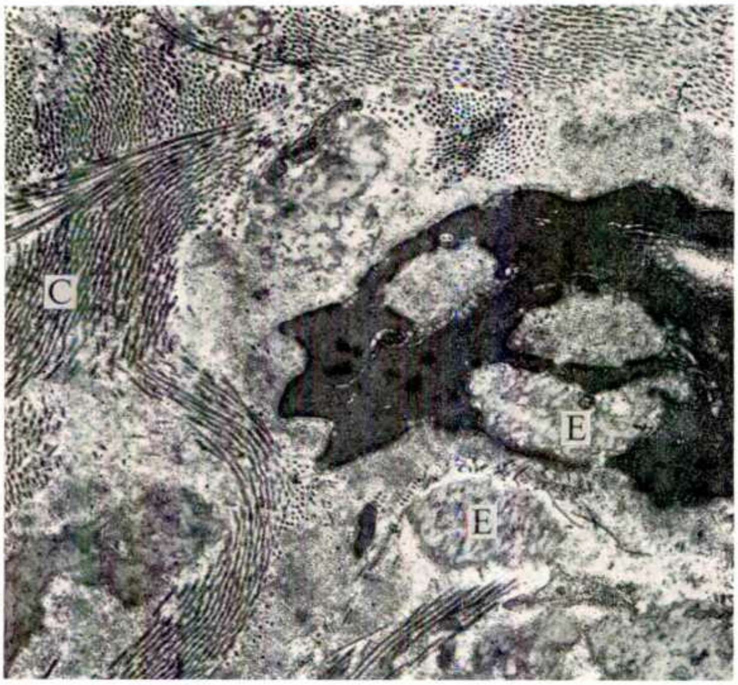

Fig. 6. An electron micrograph of the tissue described in Fig. 5 demonstrating a dense smooth muscle cell in relation to bundles of collagen and elastic fibres. A particularly close relationship between the smooth muscle cell and elastic fibres is demonstrated. × 4,8000. E—Elastic Fibre. C—Collagen.

When elastic tissue was present it was abundant and interspersed with the collagen and the smooth muscle cells (Fig. 5). Under the electron microscope typical smooth muscle cells were revealed, as well as collagen and elastic tissue. There was an intimate relationship between the smooth muscle and the elastic fibres (Fig. 6). In spite of the large amount of collagen in all these cases, there was a striking lack of fibroblasts.

(*c*) "*Congenital*" *Bulbar Strictures*

In these 3 cases the lamina propria was also widened but in the underlying tissue we found large bundles of smooth muscle within the septa dividing one cavernous blood space from the next in the corpus spongiosum (Fig. 7).

Discussion

Nothing in previously reported studies had made us expect to find so much smooth muscle and elastic fibres in the tissue from a urethral stricture, nor was it easy to understand why there should be so much connective tissue and so few fibrocytes.

There seemed to be more proliferation of smooth muscle in the inflammatory strictures with a recent history but even in those of long standing it did not entirely disappear. This unexpected role of smooth muscle in the scar of a urethral stricture is not, however, unique, for there is mounting evidence that smooth muscle is capable of laying down either elastic or collagen fibres *in vivo* or *in vitro* (Ross, 1968; Ross and Glomset, 1973) and indeed the accumulation of smooth muscle cells in the intima of arteries is now thought to be a fundamental step in the pathogenesis of atherosclerosis (Ross and Glomset, 1973). In tissue culture smooth muscle cells may be

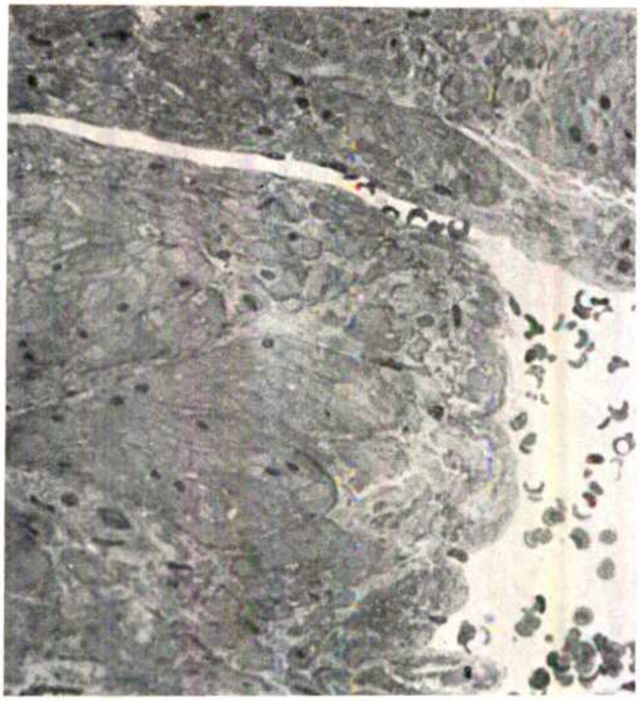

Fig. 7. A light micrograph of a 1 μm section of a congenital stricture. Large smooth muscle cell bundles are demonstrated in a trabeculum of the corpus spongiosum. Few elastic or collagen fibres are present.

provoked to lay down collagen and elastic tissue when exposed to high and low density lipoproteins such as are present in the blood of patients with atherosclerosis. For these proteins to gain access to the wall of the artery it is postulated that there must first be injury to the intimal lining—a concept clearly enunciated by Virchow (1856).

In the urethra, if a similar sequence of events takes place, one might look for some irritant agent which could make the smooth muscle cells of the urethra proliferate and lay down collagen. An obvious irritating agent in the urethra would be urine and certainly in the experimental model of the rat urethra we have found that diversion of urine away from the site of deliberate injury to the urethra permits healing to occur with minimal fibrous tissue formation (Singh and Blandy, 1975). It is no new concept in urology that less fibrosis occurs if there is adequate urinary diversion.

What then is the role of smooth muscle in urethral stricture? That smooth muscle bundles are present in the normal urethral wall (Scott and Singh, 1975), and that these could be provoked to undergo proliferation and in turn to lay down collagen or elastic fibres, offers up a wide range of possible variations in which the urethra might respond to trauma or inflammatory insult. The presence of this smooth muscle in the stricture tissue makes one speculate as to the possibility of a truly "spasmodic" stricture and the possible adjuvant role of substances known to cause smooth muscle to contract in the behaviour of the strictured urethra. One wonders whether the endemic status of urethral stricture in Uganda (Singh, 1967) may not perhaps in some way reflect the excess of 5-hydroxytryptamine known to be present in the urine of the banana-eating indigenous population (Anderson, Ziegler and Dodden, 1958) since smooth muscle contracts briskly and remains contracted for several hours when exposed to small concentrations of 5 OH-T (Gabbiani *et al.*, 1972). These speculations are now being followed up by us in the laboratory.

Whatever may be the role played by contraction of this smooth muscle in the way the stricture responds to dilatation, or to pharmacologically active substances possibly present in urine, the role it can play in laying down fibrous and elastic tissue would seem from these studies to be of basic importance in the understanding of the pathogenesis of urethral stricture, and would seem to provide anatomical evidence for Hunter's concept of an element of spasm in at least some strictures.

Summary

Biopsy material was examined from 20 urethral strictures at the time of urethroplasty, using ultramicroscopic methods not hitherto applied to the study of the pathogenesis of stricture. Abundant smooth muscle and elastic tissue was found in the post-inflammatory strictures. The scar tissue from post-traumatic strictures merely showed dense collagen.

An anatomical basis for the well known difference between the fibrous and the resilent stricture is demonstrated, and the role of smooth muscle in the development and behaviour of strictures is discussed.

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Bifid Urethra with Pre-anal Accessory Track (Y Duplication)

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Duplication of the male urethra appears in many forms though all are rare. Our overall experience will be reported elsewhere and this paper is confined to the description of one particular variety in which there is a short common stem to the urethra below the bladder neck which then bifurcates, one limb following the normal anatomical course though usually with severe stenosis, the other opening at the anal verge (Fig. 1). Most of the urine is passed from the posterior limb, sometimes with a good stream and normal control but often with a degree of obstruction. 3 cases of this description were first reported briefly in a general text book (Williams, 1968); the object of this paper is to present the details of 9 cases including the original 3 examples, additionally 2 other cases have been seen in consultation but since full details of these are not available they will not be reported here. Other cases have been described by Scott (1960), Karanjavala (1970), Selvaggi and Goodwin (1972) and Chatelain *et al.* (1973).

The Anomaly

Brief descriptions of the 9 cases are set out in the Table. Within the anatomical group there is a wide variation in the degree of obstruction. In case 1 the penile urethra, although opening through a relatively narrow meatus, could be accepted as within the normal limits for calibre but the boy had passed some of his urine from the perineal opening since birth. This posterior canal was well defined and dilated at the lower end; it was lined by transitional epithelium and surrounded by a few smooth muscle bundles. Proximally it opened to one side of the verumontanum (Fig. 2). Excision of the track left the child with normal micturition. In all other cases (Fig. 3) the anterior urethra was stenosed and micturition occurred through the pre-anal opening. Often there was a history of the passage of a few drops of urine with straining from the tip of the

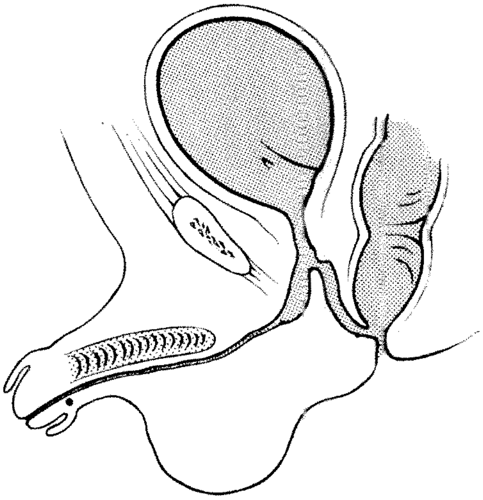

Fig. 1. Diagram to show the anatomy of the bifid urethra with perineal accessory track.

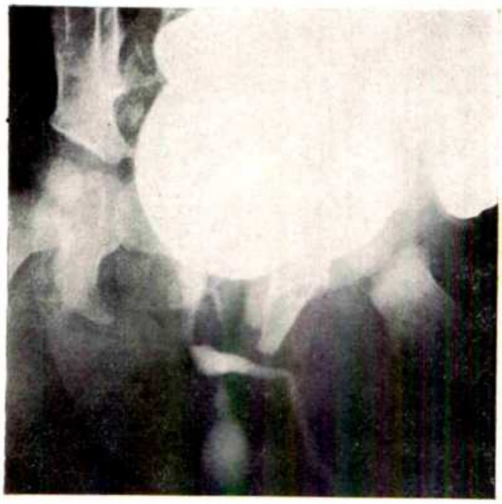

Fig. 2. Micturating cysto-urethrogram in case 1. The accessory track begins lateral to the verumontanum and has a cystic dilatation immediately above the perineal opening.

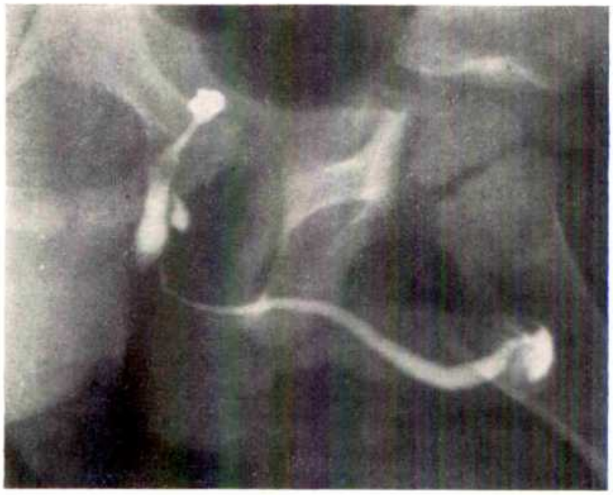

Fig. 3. Urethrogram in case 2. The normally situated urethra is stenosed in the proximal bulbar area. The posterior limb is wide and anal micturition occurs.

penis and this dysuria had led to some investigation, usually without the perineal opening being recognised at the initial study. Urethral bouginage proved impossible and was then followed by complete cessation of flow from the penis so that there was retention or passage of all urine from the perineal opening. The stenosis usually affects the urethra from the bulb to a point 1 or 2 cm short of the external meatus. The meatus itself is ordinarily normal but even the finest bougies cannot be introduced for more than 2 or 3 cm. Exploration of the atretic zone demonstrates that it is surrounded by fibro-fatty tissue without evidence of spongiosa and if an attempt is made to cut back the urethra, laying it open on to the skin as in the Johannson procedure, the lumen is lost a short distance back from the tip of the penis. The thickening of the surrounding tissues makes the Johannson approach in any case very difficult. The pathology of the stenosis is not clear but 1 case presented with a hard mass in the peno-scrotal and inguinal region which proved to be extravasation of urine (Fig. 4) which had occurred spontaneously in spite of the fact that urine was being passed from the anal urethral opening. This would suggest that there was some intrinsic defect of the wall of the urethra and to a pathological process commencing during fetal development.

The posterior channel is of variable length and calibre. Its position appears to have been

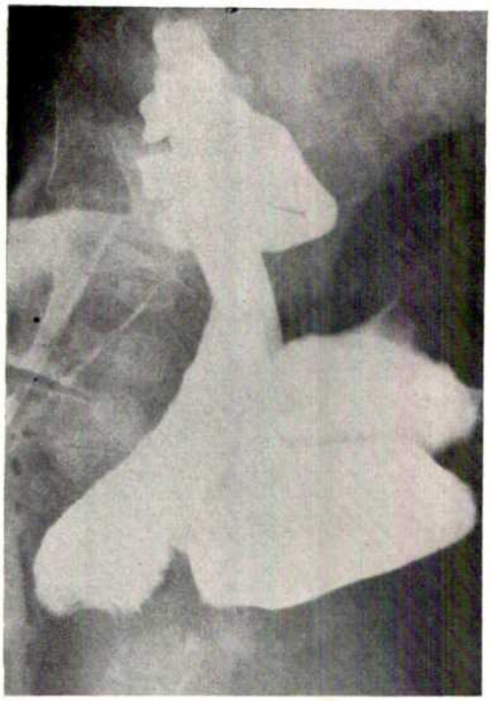

Fig. 4. Cysto-urethrogram in case 3 following the introduction of opaque medium from the perineal opening. There is reflux into dilated ureters, a normal bladder, filling of the rectum and extravasation around the obstructed anterior urethra.

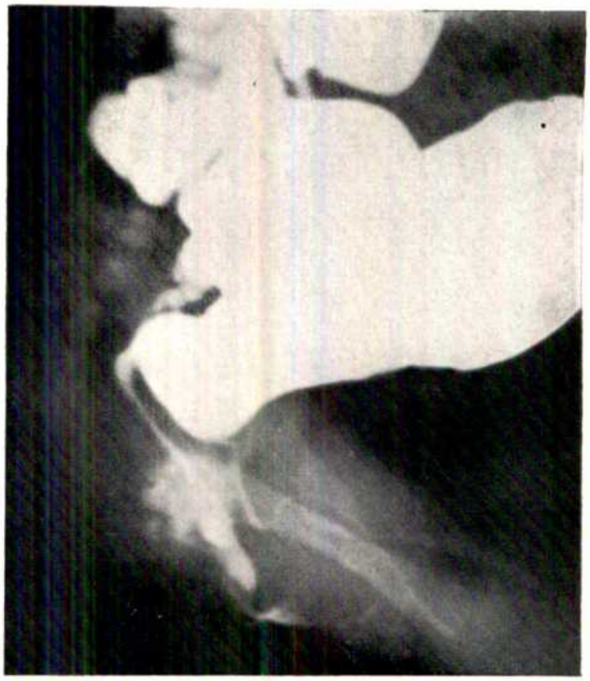

Fig. 5. Cysto-urethrogram in the same child showing the 2 urethral channels and also filling of the rectum.

relatively constant in that it takes off in the region of the verumontanum and tends to pull this area downwards and backwards so that the verumontanum itself may appear at endoscopy to lie within the posterior channel. Distally it has opened just within the anal verge or on the perineum just outside it. In Case 3 micturition from this site appeared to be entirely satisfactory, although unacceptable for a boy and in Case 9 control of this urethra was the result of the envelopment of the distal part of the track in the anal sphincter, the proximal part being wide open. Episodes of retention may occur and in some of our cases this retention was of severe degree. Where the posterior channel is very narrow it might be regarded as a fistula rather than as a urethra and if it is acceptable that a fistula may appear early in fetal life, this may well be the correct interpretation. However, the bifurcation lies well above the point of stenosis of the anterior urethra and not immediately proximal to that stenosis as might be anticipated in a simple acquired fistula. In case 1, no stenosis was present and the adult cases referred to by other authors previously listed show that the posterior channel can be the normally functioning urethra.

There may be accompanying abnormalities in the urinary tract apart from the effects of obstruction. 1 had a vesical diverticulum, 4 had reflux, 1 had a single ectopic ureter on one side with a curious additional pouch in the prostatic urethra of doubtful origin. Externally in 2 the scrotum was almost bifid with a smooth strip in the midline which incidentally facilitated repair. 2 of the cases were suffering from tracheo-oesophageal fistulae and 2 had rectal abnormalities.

Treatment

It will be apparent from the Table that those presenting at birth or soon after had severe abnormalities, whereas later cases tended to present with anal micturition as the main complaint.

Table

Case	Age	Presentation	Intravenous urogram	Cysto-urethrogram	Other anomalies	Treatment
1	1 yr	Perineal fistula	Normal	Anterior urethra normal, accessory track with cystic dilatation	Nil	Excision of accessory track
2	4 yr	Anal micturition	Normal	Normal bladder: anterior urethra narrow but permeable	Bifid scrotum	Repositioning of pre-anal opening: buried-strip hypospadias repair. Good 7-year follow-up
3	5 mth	Urinary extravasation	Bilat. hydronephrosis	Cysto-urethrogram. Bilateral reflux, anterior urethra impermeable	Bifid scrotum	Repositioning of pre-anal opening. Buried strip hypospadias repair. Good 5-year follow-up
4	3 yr	Anal micturition. Vesical calculus	Normal	Normal. Anterior urethra narrow but permeable	Partial sacral agenesisax anus.	Repositioning of pre-anal opening. Buried tube hypospadias repair. Good 4-year follow-up
5	Birth	Tracheo-oesophageal fistula (TOF)	Bilat. hydronephrosis	Gross bilateral reflux. Anterior urethra impermeable	TOF. Hirschsprungs disease—multiple complications of rectal surgery.	Cutaneous ureterostomy
6	1 mth	Uraemia	Bilateral severe hydronephrosis	Retention. Left reflux. Anterior urethra narrow but permeable	Nil	Left nephrectomy, right cutaneous ureterostomy
7	Birth	Uraemia. Tracheo-oesophageal fistula (TOF)	Bilateral severe hydronephrosis	Retention. Bilateral reflux. Both urethrae narrow but permeable	TOF. Congenital heart disease.	Died following cystostomy
8	3 yr	Anal micturition. Retention	Right pyelonephritic, left normal.	Right reflux. Vesical diverticulum. Anterior urethra impermeable	Nil	Diverticulectomy. Scrotal tube urethroplasty. Division of inter-urethral septum
9	10 yr	Anal micturition. Epididymitis	Right non-functioning, left normal.	Large irregular bladder, open bladder neck. Reflux into right ectopic ureter. Anterior urethra impermeable.	Nil	Right nephrectomy. A scrotal tube urethroplasty

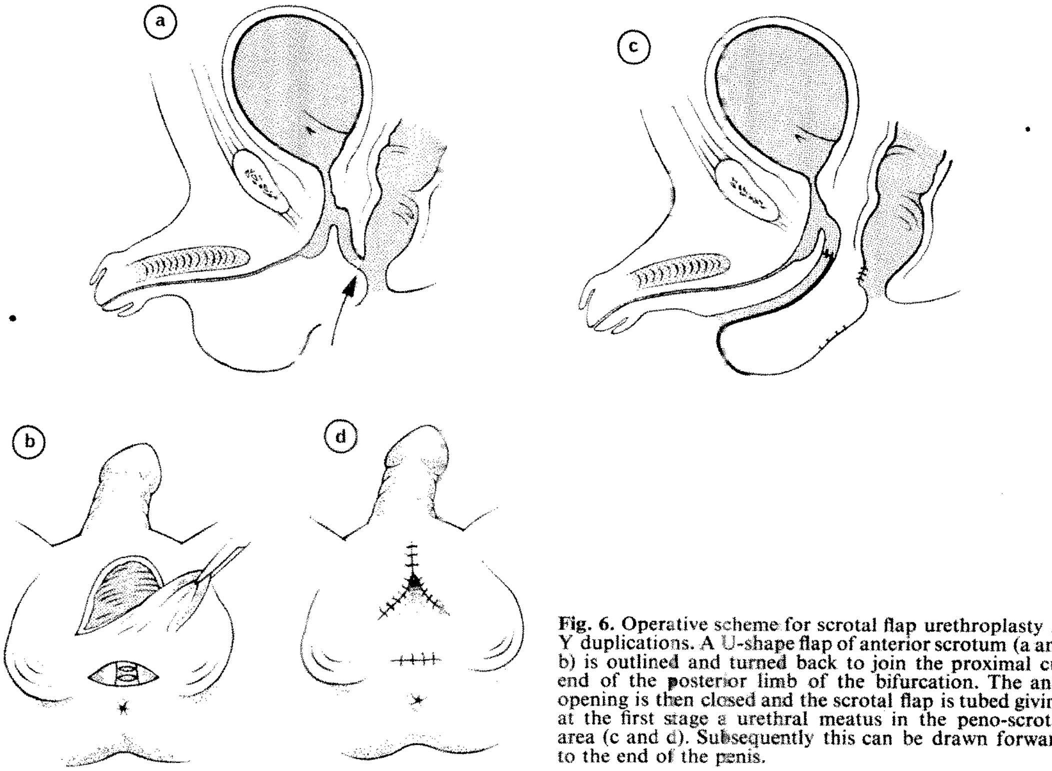

Fig. 6. Operative scheme for scrotal flap urethroplasty in Y duplications. A U-shape flap of anterior scrotum (a and b) is outlined and turned back to join the proximal cut end of the posterior limb of the bifurcation. The anal opening is then closed and the scrotal flap is tubed giving at the first stage a urethral meatus in the peno-scrotal area (c and d). Subsequently this can be drawn forward to the end of the penis.

The most severely hydronephrotic child (Fig. 5) died following needle cystostomy but congenital heart disease was probably responsible for his death. 2 children have permanent diversions on account of severe upper tract dilatation with poor ureteric peristalsis in addition to severe scarring in the region of the anal urethral opening.

In undertaking reconstructive surgery the aim has been to produce a second complete urethral channel to the tip of the penis. The atretic state of the anatomically normal channel together with its surrounding fibrosis seemed to make any attempt at a simple urethroplasty approach impossible. In 3 cases the urethral opening was at first re-positioned, transferring it from the anal verge to a point in the anterior perineum. This required colostomy for protection of healing. At the second operation a buried strip of skin extending from the perineal opening to the tip of the penis was formed into a tube and covered over as in hypospadias repair. In each case a good functioning urethra has been obtained with normal continence though the urethral opening is not quite terminal on the penis (Fig. 4). 2 cases have been treated by a scrotal flap urethroplasty without preliminary colostomy. The anal urethral opening was first divided and the posterior channel mobilised. A flap from the anterior part of the scrotum was then outlined and turned back to be anastomosed with the proximal cut end of the posterior urethral channel (Fig. 6). The anal defect was closed and good healing was secured. In 1 case, however, this operation (Fig. 7) was followed by episodes of retention due apparently to the formation of a valvular flap from the septum between the 2 urethrae. Division of this flap at the time of the second procedure to bring the urinary meatus to the tip of the penis relieved this symptom but control in this case is not yet perfect. None of the children has any serious chordee and there does not appear to be any interference with erection. No information has been obtained as to sexual function though the testicles have been clinically normal in all cases.

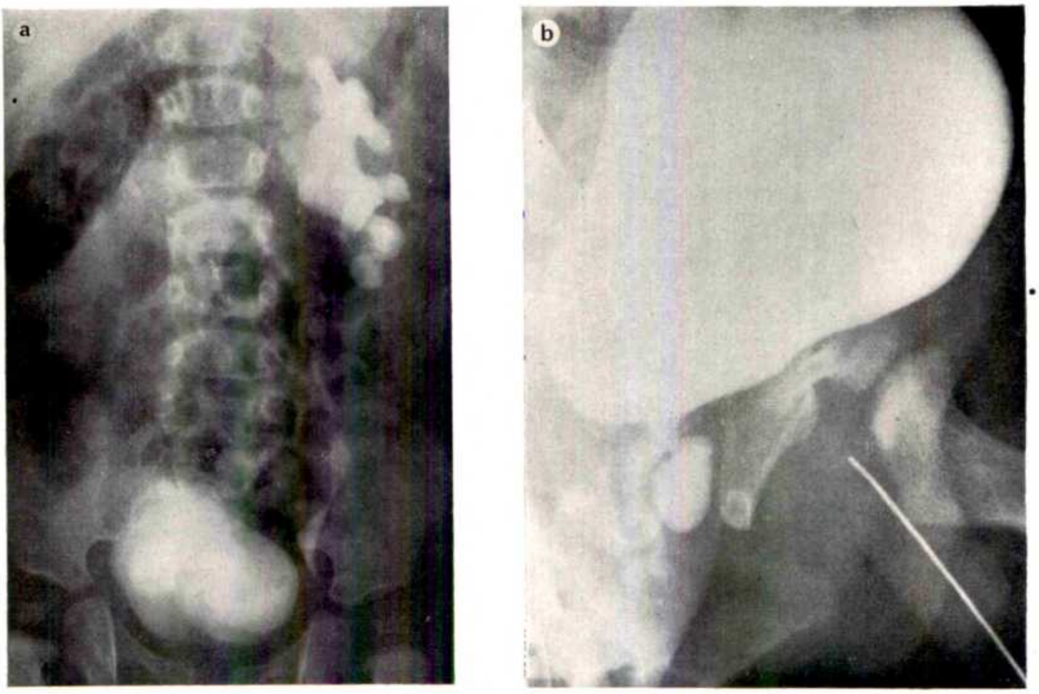

Fig. 7. (a) Intravenous pyelogram in case 8 showing vesical diverticulum and poor renal function. (b) Cysto-urethrogram showing the urethral bifurcation: the anterior limb is dilated above the obstruction in the bulbar region. The posterior limb is of good calibre. Following the first stage of reconstruction the septum between the 2 channels formed a valvular obstruction and had to be resected.

Summary

Bifid urethra with a pre-anal or perineal accessory track (Y duplication) is an abnormality insufficiently recognised and its true anatomy may be overlooked. 9 cases are reported together with a description of an operative correction.

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Sexual Function in Hypospadiacs

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The incidence of hypospadias in the general population is often estimated at 1 : 350 (Farkaš, 1967). Hypospadias is therefore not a very rare condition and the long-term follow-up of the sexual function in treated patients must be of interest. In 1971 Ericsson and Hedenberg reported such a study on a group of Swedish patients. They found that their sexual function deviated from normal; coitus experience was frequently delayed and penile hypoplasia was common. The results of the present study differ from those of Ericsson and Hedenberg.

Patients

Patients over 18 years of age who had been operated on for hypospadias many years previously at the Hospital for Sick Children, Great Ormond Street and St Peter's Hospitals, London, were sent a questionnaire form to fill in. Details of their original condition and operation were available. The information requested included their marital status, whether they had children or whether they had been investigated for infertility. They were also asked about their sexual experience and at what age they had had their first sexual intercourse, whether their erection and ejaculation were satisfactory and whether they were satisfied with the appearance and size of their penis. Finally they were asked whether they had any difficulty of micturition or in directing the stream and whether urine came from the tip of the penis or not. The patients were encouraged to present themselves for examination. Investigations were done as necessary.

Out of 351 patients 82 returned the questionnaire forms (23·4%). 2 patients were known to have died of malignant disease. Most of the remaining letters were returned undelivered because the patients had moved away many years before. An attempt to trace the whereabouts of a sample of 14 of these patients through the Local Health Authorities was unsuccessful.

47 of the 82 patients (57·3%) were under 23 years of age (Fig. 1).

Analysis of the Data obtained from the Case Notes

Degree of Hypospadias

The hypospadias was classified as glandular, coronal, penile, penoscrotal, scrotal or perineal. Penile hypospadias was further subdivided into distal penile, midpenile and proximal penile depending on which third of the penis carried the urethral meatus. Distal penile hypospadias was the commonest variety (42·7%, Table I). All scrotal and perineal cases had normal male chromosomal pattern.

Chordee

Ventral curvature of the penis was present in 28·6% (2/7) of patients with glandular hypospadias, in 37·5% (6/16) of patients with coronal hypospadias, in 60% (21/35) of patients with distal penile hypospadias and in all patients with midpenile or a greater degree of hypospadias (Fig. 2). It was marked in all the scrotal and perineal cases.

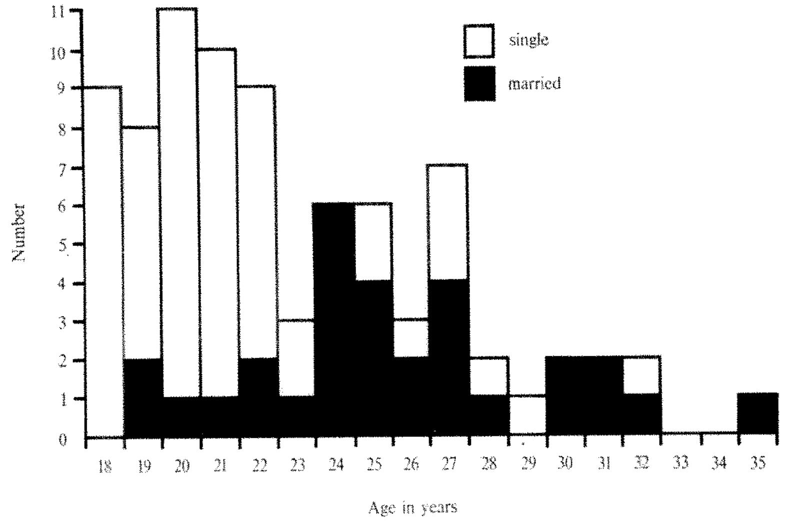

Fig. 1. Histogram showing age distribution and marital status of the 82 treated hypospadiacs.

Associated Conditions

Undescended testicles were the most common association occurring in 6 cases (7·3%); bilateral in 4. There was no particular association with the degree of hypospadias. All were successfully operated on.

Monorchism, confirmed by laparotomy, occurred in a case with scrotal hypospadias. Covered anus with scrotal fistula occurred also in 1 case. 3 patients had had a congenital inguinal hernia and 1 a congenital hydrocele.

Primary Operations for the Hypospadias (Table II)

73 of the patients had had their definitive operation in early childhood (89%), 4 in later childhood and 5 during adolescence:

1. The 2-stage Denis Browne (1949) buried skin strip repair was used in 51 cases (62·2%). In the first stage of chordee correction a dorsal penile release incision was routine.
2. The second stage of a Denis Browne (DB) repair was used in 14 cases; all but 1 had had no chordee.
3. The Ombrédanne repair (1911) was used in its 2 stages for 2 patients.

Table I

Degree of Hypospadias (82 Cases)

Degree	Number	Percentage
Glandular	7	8·5
Coronal	16	19·5
Distal penile	35	42·7
Midpenile	7	8·5
Proximal penile	5	6·1
Penoscrotal	5	6·1
Scrotal	6	7·3
Perineal	1	1·2

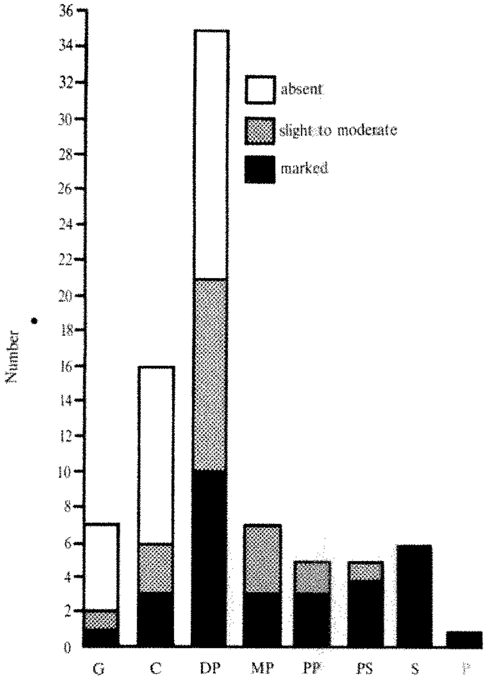

Fig. 2. Histogram showing the incidence and degree of chordee in the 82 hypospadiacs. G = glandular, C = coronal, DP = distal penile, MP = midpenile, PP = proximal penile, PS = penoscrotal, S = scrotal and P = perineal hypospadias.

4. The Denis Browne meatotomy, cutting the septum between the urethra and the blind duct dorsal to it, was used in 33 patients with meatal stenosis. In 15 it was the only procedure done.

Analysis of the Data obtained from the Questionnaire Sheets

Sexual Experience

Of the 82 hypospadiacs 63 (76·8 %) had had sexual intercourse; 34 of these (54 %) before the age of 19 years (Fig. 3). The age distribution of the 19 patients without sexual experience is shown in Table III.

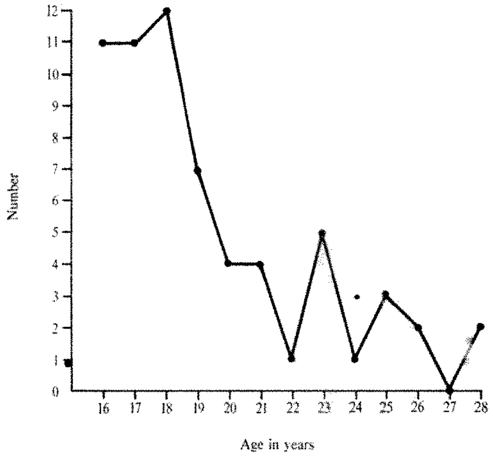

Fig. 3. Diagram to show the age at first sexual intercourse in 63 treated hypospadiacs.

Table II

Primary Operative Procedures for 82 Hypospadiacs

Hypospadias	Chordee	DBR	DB II	Ombrédanne	DBM*
Glandular (7)	Absent (5)	...	...	...	5
	Present (2)	2	...	...	...
Coronal (16)	Absent (10)	...	3	...	7
	Present (6)	6	...	...	...
Distal penile (35)	Absent (14)	...	10	2	3
	Present (21)	19	1	...	...
All others (24)	Present (24)	24	...	...	...
Total	82	51	14	2	15

* Patients who had further primary operative procedures following the meatotomy are excluded. DB = Denis Browne, R = Repair, II = second stage, M = meatotomy.

Table III

Age Distribution of 19 treated Hypospadiacs with no Sexual Experience

Age in years	18	19	20	21	22	23	24-26	27
Number	5	3	4	2	2	2	0	1

Marital Status

30 of the 82 patients were married (Fig. 1). The median age at marriage was 22 years. 15 had children and 12 were married but were not yet trying to raise a family. 3 were married and had failed to get children; 1 was azoospermic and 2 had oligospermia.

Appearance and Size of the Penis

3 patients felt that their penis was small. They all had had bilateral orchidopexy and their penile size had then been recorded as small; none of them presented for examination. All 17 patients who were examined were found to have normal-sized penises according to the measurements given by Masters and Johnson (1966).

11 patients were not satisfied with the shape of their penis. 4 of these had a ventrally curved penis; they all required reoperation. 7 patients were not satisfied with a redundancy of their distal penile skin: 4 were not unduly concerned; another was not advised surgery and the last 2, 1 also with a small penile fistula, needed operation.

Penile Erection

77 patients (93·9 %) had satisfactory erection. 1 had unsustained erections; his plasma testosterone levels were normal. 4 had unsatisfactory erections due to curvature of the penis: 2 were married, 1 causing his wife severe discomfort on intercourse, and the other 2 had sexual experience. All 4 patients had moderate chordee of the flaccid organ. 2 of them had originally been operated on

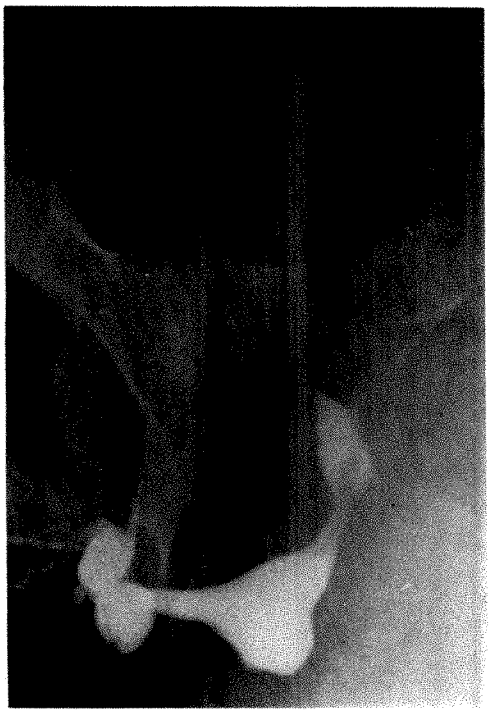

Fig. 4. Urethrogram demonstrating the large diverticulum arising from the floor of the bulbar urethra.

for moderate chordee. Another had had his distal penile hypospadias with slight chordee operated on only by a second stage DB repair. The fourth, also with a distal penile hypospadias, had been described as having no chordee; he only had a DB meatotomy done.

Ejaculation

77 patients (93·9 %) had satisfactory ejaculation. Of the remaining 5 patients, 1 could not ejaculate due to a large urethral diverticulum acting as a seminal receptacle (Fig. 4). 4 had slow, weak ejaculation due to, in one case each, a urethral diverticulum, a utricular diverticulum, a wide bulb urethra and a distal urethral stricture.

Difficulty of Micturition

In 46 patients (56·1 %) the urethral meatus was situated at the tip of the penis and there was no difficulty during micturition although 3 patients, 2 with the urethral diverticula and 1 with the wide bulbar urethra, needed to expel a small volume of urine by perineal pressure at the end of micturition.

36 patients (43·9 %) passed urine from underneath the glans: 20 had no urinary difficulty and 13 needed to direct their stream. Of the remaining 3 patients, 1 with moderate chordee could not direct the stream from a standing position, 1 with a distal penile fistula sprayed at micturition and 1 had a weak stream due to a urethral stricture.

Discussion

Ericsson and Hedenberg (1971), in their questionnaire survey of 62 Swedish patients operated on for hypospadias, found later than normal age at first sexual intercourse. In the age group

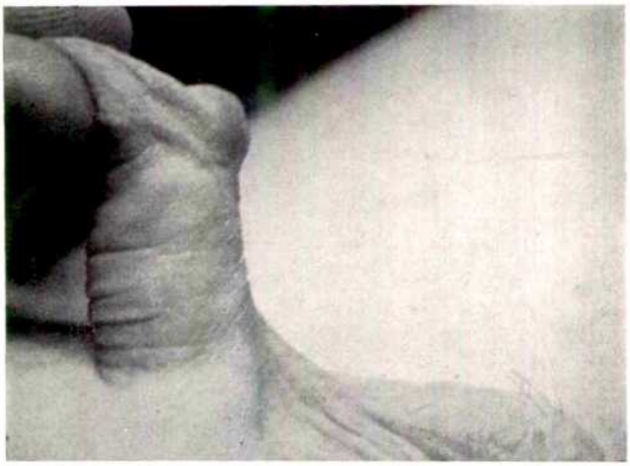

Fig. 5. A faulty technique in testing for chordee.

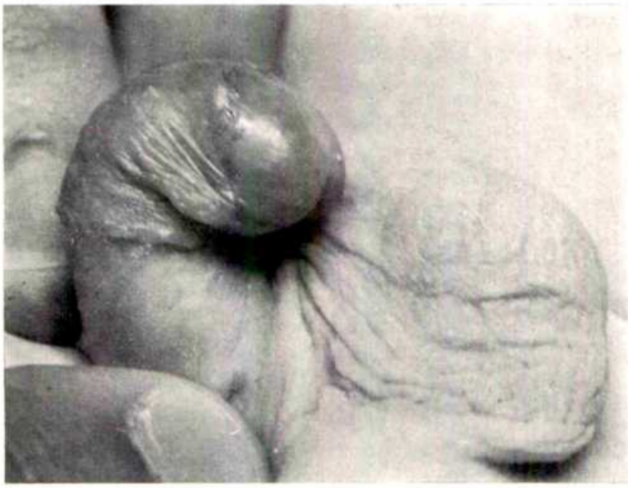

Fig. 6. Same patient as in Fig 5 demonstrating the chordee unveiling test.

18 to 20 years 62% of their series had had sexual intercourse compared with 80% in normals and in the age group 21 to 25 years 69% had had intercourse compared with 93%. In the present series 41·5% (34/82) had intercourse by the age of 18 compared to 34% in normal British males (Schofield, 1965). In contradiction to Ericsson and Hedenberg, therefore, hypospadiacs operated on were not subject to a delay of their first sexual experience. In addition the median age at marriage in this group is similar to that for the population in England and Wales (Kiser, 1959).

The patients with coitus experience in Ericsson and Hedenberg's study (1971) formed only 59·7% (37/62) of the total compared with 76·8% (63/82) in this series; their survey, however, included 7 patients below 18 years of age. In their survey 18·9% (7/37) of those with coitus experience had difficulties caused by an unsatisfactory erection, while in this study 15·9% had sexual difficulties (10/63), only half of which were due to unsatisfactory erection (7·9%). 1 of these patients had poor erections of psychologic origin and 4 (6·3%) had penile curvature. 2 of the latter were due to inadequate correction of the chordee or its recurrence but 2 had had no chordee correction; 1 had been considered originally to have slight chordee and the other to have none. On examination both had moderate chordee and this emphasises the value of the accurate clinical assessment of chordee and the importance of its correction in all cases, including

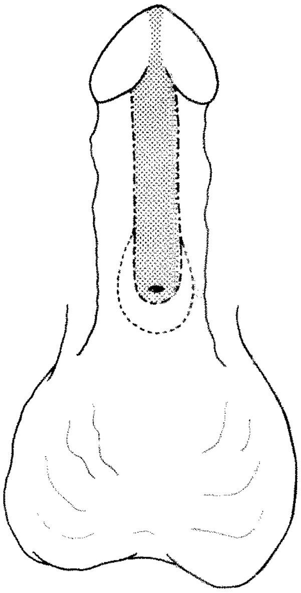

Fig. 7. Illustration to show the correct (shaded area) and faulty (dotted outline) techniques in fashioning the strip of skin to be buried or tubed in hypospadias repair.

those of a slight degree. This opinion is further strengthened by the statement of Farkaš (1967), that slight chordee found at birth becomes more marked at puberty.

Examination for chordee by suspending the penis from the prepuce is faulty (Fig. 5). I also do not agree with Farkaš (1967) that examining the penis in the erect state is the only way to reveal small degrees of curvature. The presence and degree of chordee is easily judged by the Innes Williams test (the chordee unveiling test): the skin over the shaft of the penis is slid downwards towards its base using the thumb and index of the left hand (or fingers of both hands). The test is inaccurate if the prepuce is not fully stretched by the pull on the penis skin (Fig. 6).

The other 5 patients with sexual disturbance had trouble only with ejaculation. One of these had a utricular diverticulum as a congenital abnormality and another had a distal urethral stricture. The remaining 3 had large postoperative urethral diverticula or dilatation. Farkaš (1967) believed that such postoperative diverticula were the result of dilatation of the normal urethra proximal to a strictured neourethra. In this series diverticula or dilatation occurred at the proximal end of the hypospadias repair without the presence of stricture. This leads me to believe that the fault occurred at the time of surgery in gauging the width of the buried skin strip; its width should be both adequate and uniform. If one is generous in estimating the width of the strip proximally there will be a tendency to proximal diverticulum formation (Fig. 7). Also the incision around the inferior margin of the urethral meatus should be 2 mm away; if a wider strip of skin is left a postoperative diverticulum is again predisposed to (Fig. 7). These details in technique will also apply to the buried skin tube modification of the Denis Browne repair.

Only 3 of the patients in this series (3·7%) were concerned about the small size of their penis although this did not prevent satisfactory intercourse. This low incidence of penile hypoplasia is in marked contrast with the findings of Ericsson and Hedenberg (1971) who report that over 50% of their patients (32/62) described their penis as being of small size although preoperatively only 19·4% (12/62) were recorded as having penile hypoplasia. Farkaš (1967) found penile hypoplasia preoperatively in 33·9% of 505 hypospadiacs and states that correcting the chordee improves the further development of the penis. His statement throws additional doubt on the findings of Ericsson and Hedenberg (1971).

Summary

The sexual function of 82 patients treated for hypospadias was assessed. It was concluded that the sexual function in these patients was unsatisfactory only following incomplete or incorrect surgery. The aim of surgery should be to achieve a straight penis with an adequate urethral lumen and a urethral orifice situated at the tip of the glans. Proper assessment of chordee and meticulous care in surgical technique are the prerequisites for success. They are the only preventive measures of the physical, psychic, sexual and social handicaps to which hypospadiacs are subjected.

I wish to thank Mr D. Innes Williams, Dean of the Institute of Urology, for his kindness and constant help throughout this study, Professor A. Wilkinson of the Institute of Child Health for allowing me to follow up the patients of the late Mr Denis Browne, the staff of the Medical Records departments at the Hospital for Sick Children and St Peter's Hospitals (London) for their help, Miss F. Wadsworth for the illustrations, Mr R. Bartholomew for the photographs and Miss Anthea Minchom who typed the manuscript.

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Transplantation of Interstitial Cells of the Testis: Effect of Implant Site, Graft Mass and Ischaemia

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The earliest reported work on the endocrine effect of testicular transplantation is that of Berthold (1849) who noted that, following intraperitoneal grafting in the cock, atrophy of secondary sexual characters did not occur after castration. Grafting by vascular anastomosis has been attempted (Lee, Tung and Orloff, 1971) but it is not practicable because of the small size of the vas and vessels involved. Transplantation of small amounts of testicular tissue in the free state was therefore tried, allowing oxygen to reach the grafted tissue by diffusion until vascularisation occurred. Preliminary results (Fox, Boyle and Hammonds, 1973) showed that following autotransplantation of testicular homogenate in the mouse interstitial cells survived whilst spermatogenic tissue atrophied.

The aims of the present investigation were:

1. To locate the optimum site for implantation.
2. To determine the minimum quantity of testicular tissue required for androgenic effect.
3. To find the effect of ischaemia on the survival and subsequent function of the interstitial cells under various conditions of storage.

Materials and Methods

Young adult (CBA-T6T6 × C57BL) F_1 hybrid mice were used. The technique for removal and autotransplantation of the testes has been described fully elsewhere (Fox, Boyle and Hammonds, 1973).

Optimum Site. The diced tissue from both testes was transplanted subcutaneously to the trunk (dorsal site), into the ear lobe or intraperitoneally.

Minimum Quantity. 100 mg (approximately, from 2 testes), 20 mg or 5 mg of testicular tissue was implanted either subcutaneously or intraperitoneally.

Ischaemia. Following removal and dicing, the testicular tissue was placed in 3 ml of T.C. 199 and incubated for periods between $\frac{1}{2}$ and 48 hours at 0 to 4°C (mean 3°C) room temperature (mean 21°C) and 37°C. During this time the suspension was intermittently agitated. After the required period of ischaemia the testicular tissue was transplanted subcutaneously into the original donor.

Effects were assessed after 3 months by relative seminal vesicle and penis weights and histological examination of the grafts, seminal vesicles and prostate glands. The relative seminal vesicle weight was expressed as a ratio of the seminal vesicle weight to body weight. The results following autotransplantation were compared with those obtained in sham operated and castrated controls. In the sham operated mice the operative procedure was the same except that the testes were not removed.

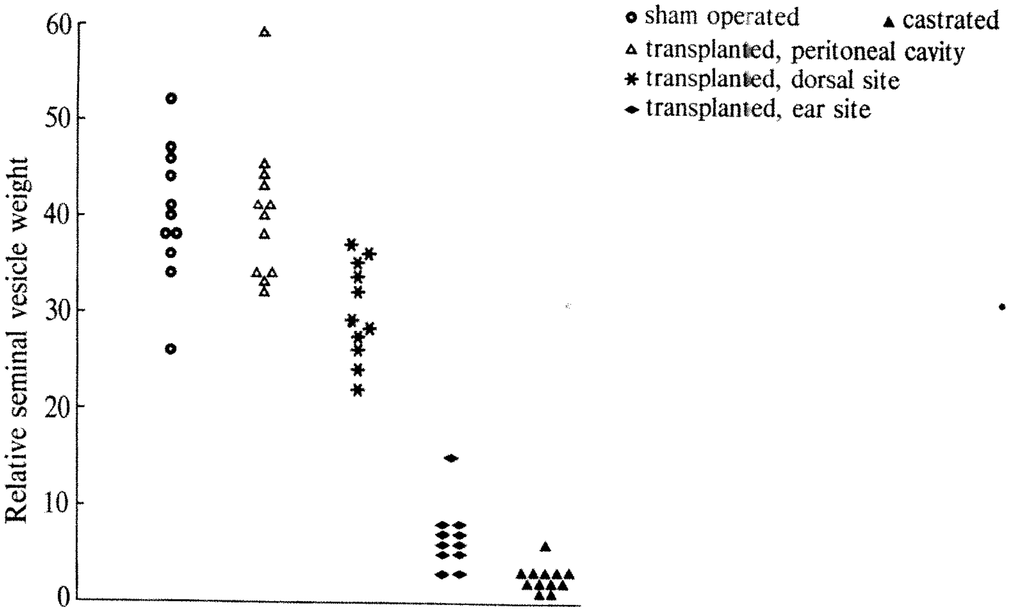

Fig. 1. Relative seminal vesicle weights of adult (CBA-T6T6 × C57BL) F_1 hybrid mice 3 months after operation.

Results

Optimum Site. In the sham operated animals the vesicle weights remained the same as in normal mice but following castration seminal vesicles atrophied. After castration and transplantation the weight of the vesicles varied according to the site used for grafting (Fig. 1). The relative seminal vesicle weights of all transplanted animals were significantly higher than those of castrated controls ($P<0{\cdot}05$) but only in the group given intraperitoneal grafts were the weights comparable to those of sham operated mice ($P<0{\cdot}5$). The ear pinna was the least effective site. The penis weights followed the same pattern.

Histological examination of the subcutaneous grafts at 3 months showed large collections of interstitial cells with complete atrophy of the seminiferous tubules (Fig. 2). There appeared to be fewer cells in the ear lobe grafts than in the dorsal subcutaneous grafts. Histological examination of the intraperitoneal grafts was not performed as these could not be identified macroscopically. In the castrated animals the seminal vesicles showed complete atrophy with decreasing size of the columnar epithelial cells and minimal secreted fluid in the lumen (Fig. 3). The seminal vesicles of the grafted animals were similar to those of the controls, both distended with secreted fluid and lined by tall vacuolated columnar epithelial cells (Fig. 4). After castration the prostate showed the glands to contain flattened cells with no evidence of secretion in the lumina (Fig. 5). In the prostate glands of the transplanted animals marked budding of the epithelial cells was seen together with evidence of ample intraluminar secretion (Fig. 6).

Minimum Quantity. Figure 7 shows the relative seminal vesicle weights of the castrated mice given 5 mg, 20 mg or 100 mg of testicular tissue intraperitoneally (I.P.) or subcutaneously (S.C.) and compared with castrated and sham operated mice. Following subcutaneous transplantation of 5 mg. of testicular tissue seminal vesicle weights were not significantly higher than those of castrates ($P>0{\cdot}2$) but in all other groups, including those given 5 mg of tissue intraperitoneally, the weights were higher. There was good correlation between quantity given and resulting vesicle

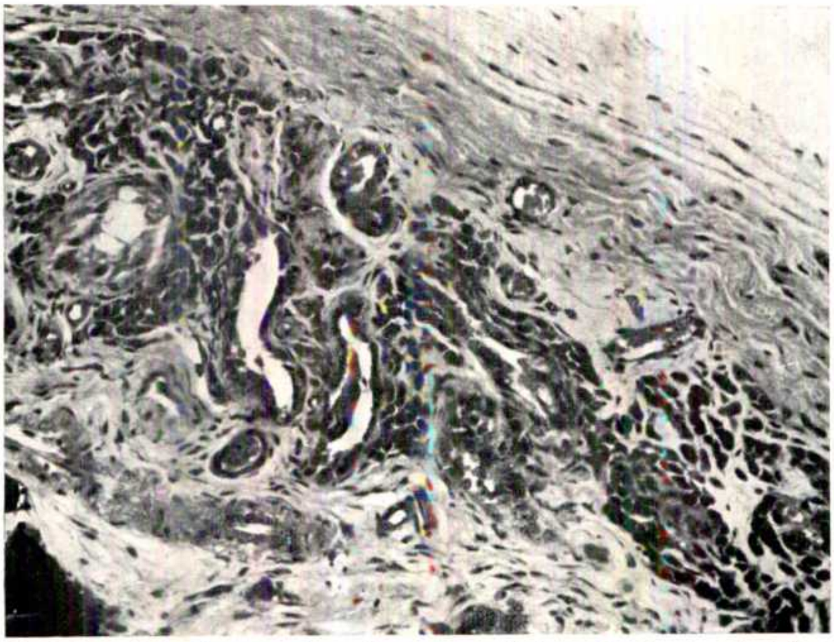

Fig. 2. Interstitial cells present in a subcutaneous graft 3 months after transplantation. Atrophy and calcification of seminiferous tubules. H. and E. × 100.

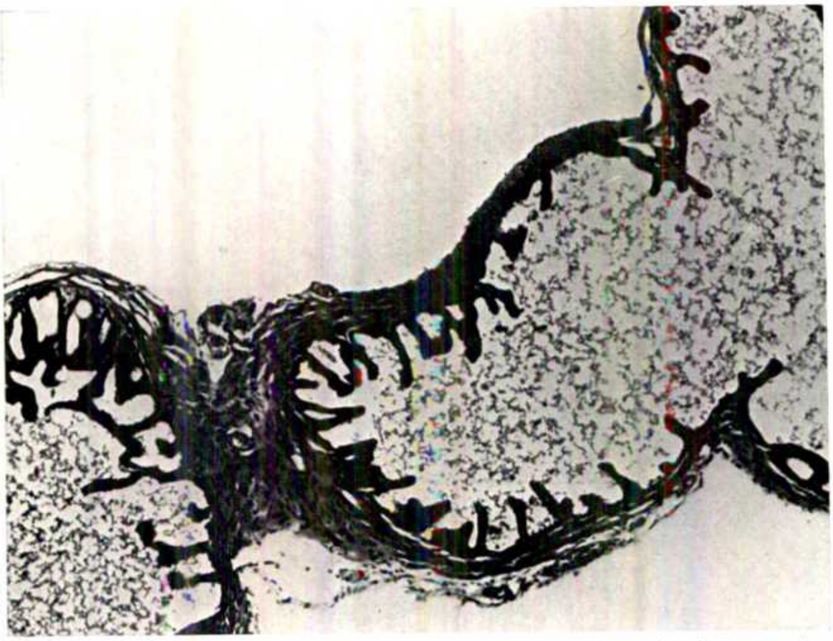

Fig. 3. Section of a seminal vesicle from a young adult mouse 3 months after castration. H. and E. × 40.

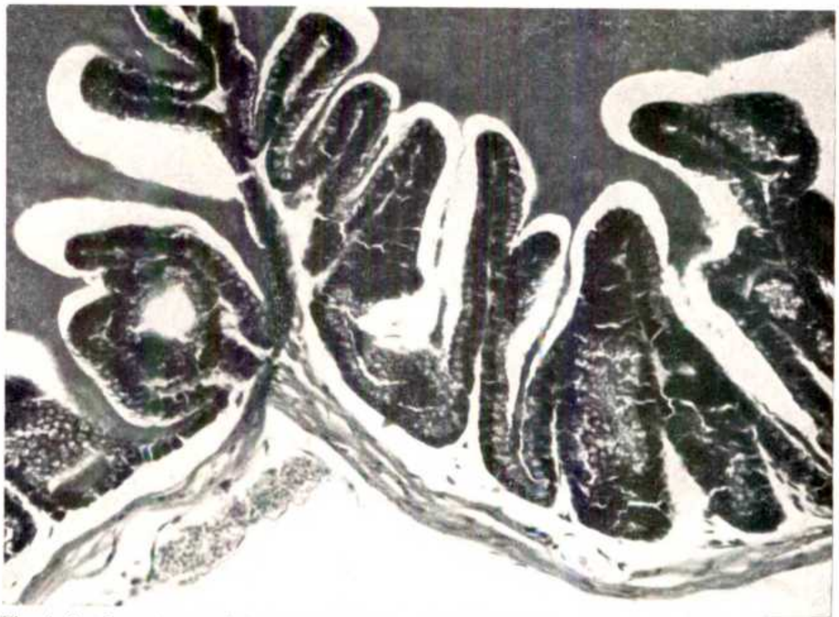

Fig. 4. Section of a seminal vesicle from a young adult mouse 3 months after castration followed by successful subcutaneous grafting of testicular tissue. H. and E. × 100.

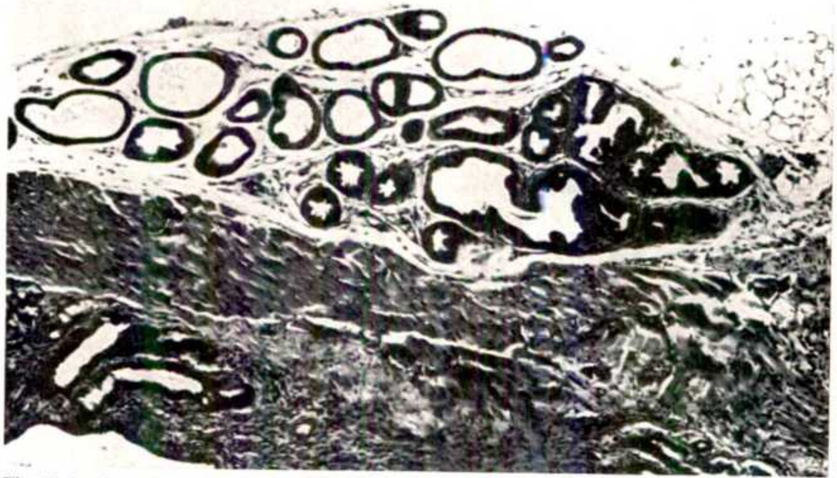

Fig. 5. Section of prostate gland from a young adult mouse 3 months after castration. H. and E. × 40.

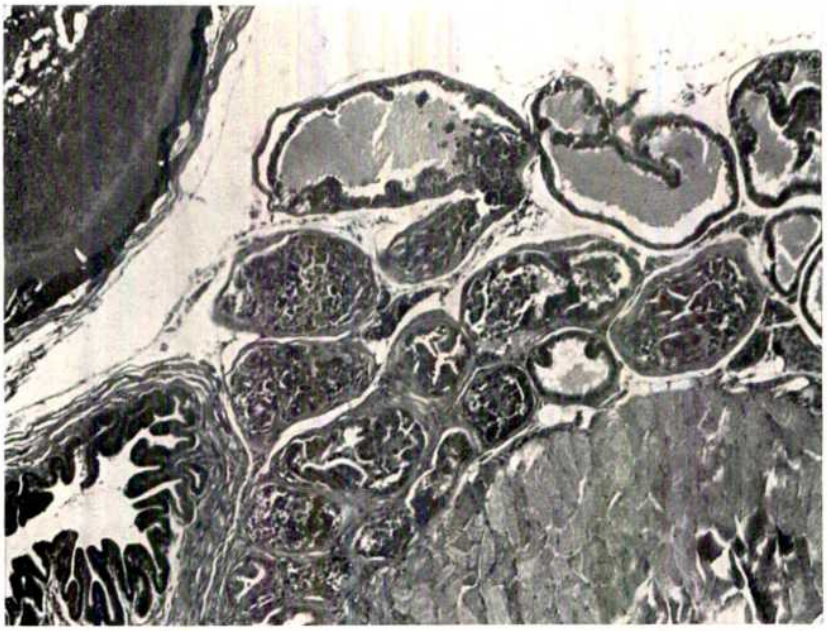

Fig. 6. Section of prostate gland from a young adult mouse 3 months after castration followed by successful subcutaneous grafting of testicular tissue. H. and E. ×40.

weight and results were always better after I.P. than after S.C. implantation. There was no significant difference in the seminal vesicle weights between the groups given 5 mg I.P. and 20 mg S.C. ($P > 0{\cdot}2$). The penis weights showed the same general pattern as the seminal vesicle weights.

Effect of Ischaemia. The results 3 months after grafting are shown in Figures 8, 9 and 10. The relative seminal vesicle weights remained above those of castrated mice at all times following ischaemia at 0 to 4°C (mean 3°C) up to and including 48 hours ($P < 0{\cdot}001$), although there was some decrease after 8 hours. At room temperature (mean 21°C) the relative seminal vesicle weights were above castrate levels following 12 hours' ischaemia ($P < 0{\cdot}001$) but not after 24 hours ($P > 0{\cdot}2$). The relative seminal vesicle weights reached those of castrated animals following 4 hours ischaemia at 37°C ($P > 0{\cdot}9$). After 1 hour the weights were already lower than those after zero time ischaemia.

Discussion

The experiments described in this paper confirm previous findings (Fox, Boyle, and Hammonds, 1973) that autotransplantation of homogenate suspensions of the mouse testis in the free state is possible. Interstitial cells survived and functioned while spermatogenic tissue atrophied. Both subcutaneous and intraperitoneal injection were successful. The dorsal subcutaneous site was more effective than transplantation into the ear pinna but the intraperitoneal route was the most efficient of all. It is likely from the results obtained that the interstitial cells were scattered widely throughout the peritoneal cavity and became attached to the mesothelial lining allowing

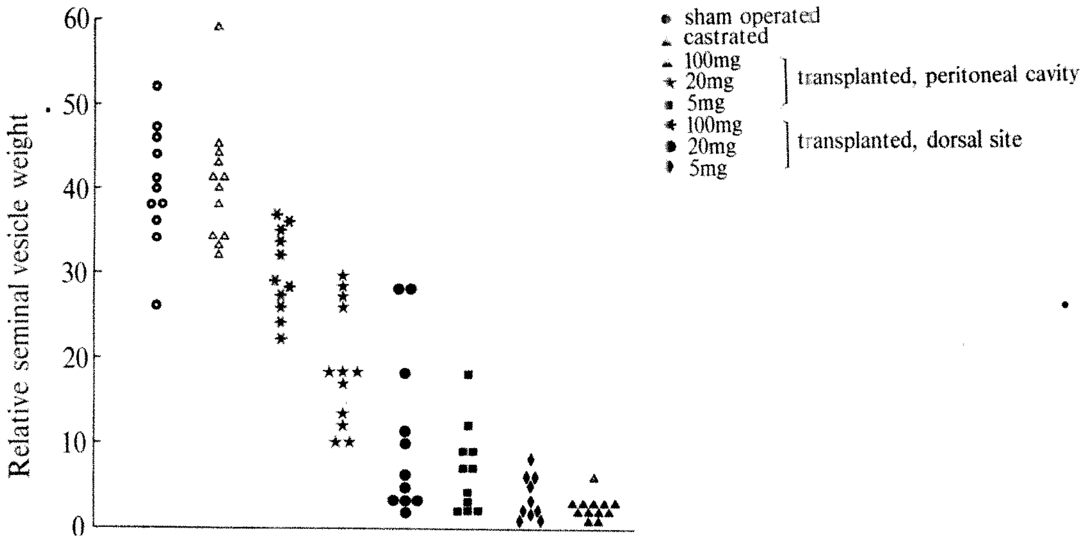

Fig. 7. Relative seminal vesicle weights of adult (CBA-T6T6 × C57BL) F_1 hybrid mice given various quantities of testicular homogenate.

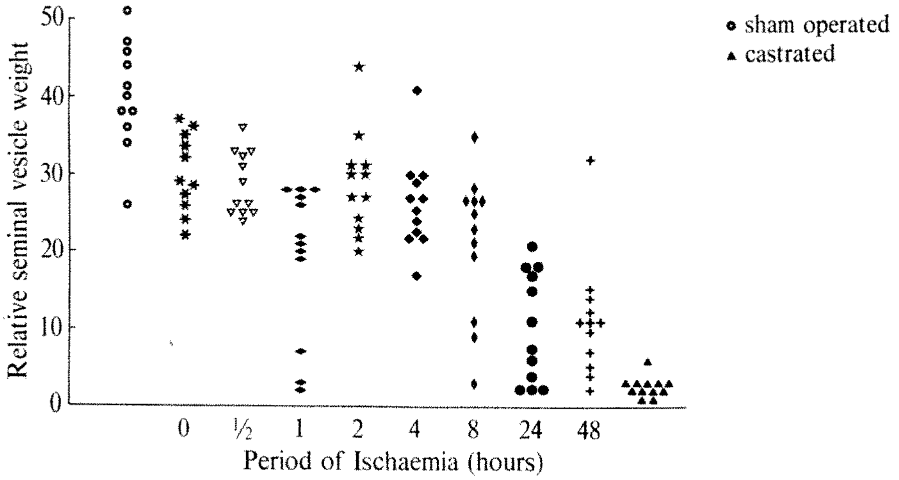

Fig. 8. Relative seminal vesicle weights of adult (CBA-T6T6 × C57BL) F_1 hybrid mice given testicular homogenate grafts following varying periods of ischaemia at [illegible]°C. ∗ ▽ ✦ ★ ◆ ♦ ● + transplanted, dorsal site.

vascularisation to occur. The ear pinna was the least effective site, probably because of the localised area into which the injection could be made and its relatively poorer blood supply.

As little as 5 mg testicular tissue, which constituted 5 % of the weight of both gonads, was effective in producing some significant androgenic effect at 3 months when given intraperitoneally. Whether hyperplasia of the transplanted cells occurs in relation to need will be the subject of a further communication. More tissue was required for subcutaneous grafting than for intraperitoneal injection to achieve the same effects.

Interstitial cells were remarkably resistant to the effects of ischaemia and it is this property which probably allows them to survive while spermatogenic tissue dies. It is probable that the

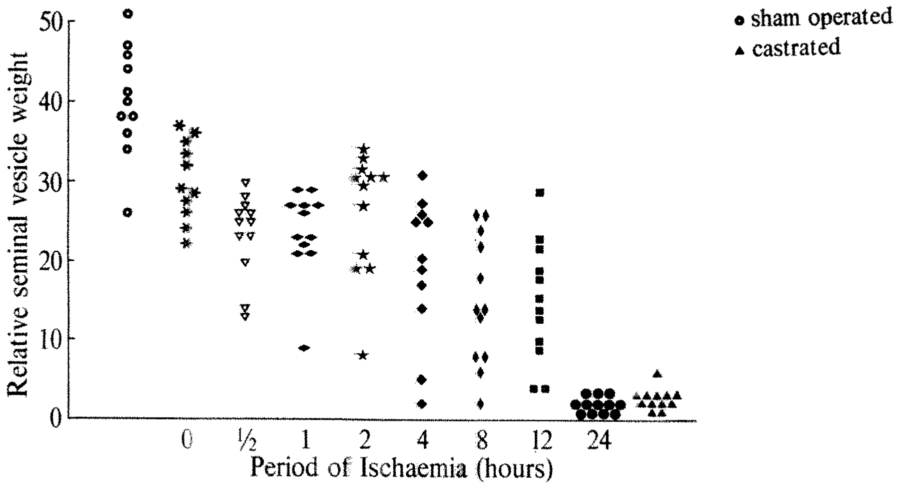

Fig. 9. Relative seminal vesicle weights of adult (CBA-T6T6 × C57BL) F_1 hybrid mice given testicular homogenate grafts following varying periods of ischaemia at 21 °C. * ▽ ✦ ★ ◆ ♦ ■ ● transplanted, dorsal site.

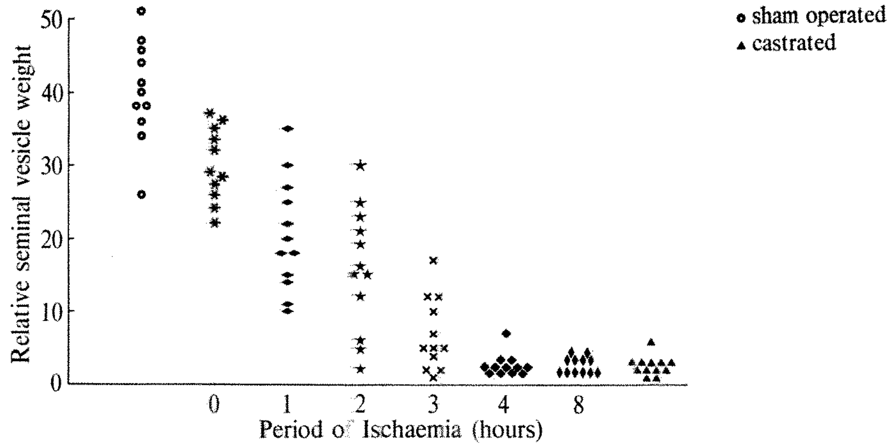

Fig. 10. Relative seminal vesicle weights of adult (CBA-T6T6 × C57BL) F_1 hybrid mice given testicular homogenate grafts following varying periods of ischaemia at 37 °C. * ✦ ★ × ◆ ♦ transplanted, dorsal site.

spermatogenic cells cannot withstand survival in the free state following interruption of the blood supply up to the time when re-vascularisation occurs. Survival and continuing function of interstitial cells was found as long as 3 hours after incubation at 37°C, 12 hours at 21 °C and 48 hours at 3°C. The effect gradually diminished but was still significant at the end of these periods, in comparison to that of castrates.

If it is possible to extrapolate from the animal model to the human, there are 2 clinical possibilities. Firstly, following traumatic orchidectomy, implantation after a period of ischaemia could be performed. Secondly, in bilateral testicular undescent, which cannot possibly be corrected by surgery, the patient's own testes could be removed and grafted. If interstitial cells survived, normal androgenic activity would be maintained. The concomitant destruction of spermatogenic cells would be of advantage as it would eliminate the increased incidence of neoplasia which is known to occur in these organs.

Summary

Autotransplantation of testicular tissue was performed in inbred mice to subcutaneous trunk, ear lobe and intraperitoneal sites.

The results were assessed after 3 months by determining the weights of seminal vesicle and penis and by the histological appearances of the grafts and seminal vesicles.

Intraperitoneal implantation produced maximal effects and as little as 5 mg of testicular tissue could be grafted with demonstrable androgenic action on the host.

Spermatogenic tissue atrophied in all cases but interstitial cells were shown to survive and function 3 months after subcutaneous grafting following 48 hours ischaemia at 3°C, 12 hours at 21°C and 3 hours at 37°C.

We wish to thank the Medical Research Council for financial support and the Department of Photography at the Sheffield Royal Hospital for help with the illustrations; also Miss S. Geary and Miss L. Lansdale for assistance with the histology.

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200 Infertile Males: Correlation of Chromosome, Histological, Endocrine and Clinical Studies

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In many cases of male infertility the exact cause of relative or complete failure of spermatogenesis is unclear. Although seminal analysis is often improved by treatment, at least 30% of patients do not respond well and the pregnancy rate may be rather disappointing (Hendry *et al.*, 1973). In 1966, McIlree *et al.* showed that 10% of 50 subfertile males had structural chromosome abnormalities in testicular preparations and they suggested that studies of meiotic chromosomes could be of considerable value to the clinician concerned with the management of male subfertility.

In order to define the incidence and importance of disorders of meiosis as a fundamental cause of infertility, somatic and meiotic chromosomes have been studied blindly and prospectively, in parallel with systematic and multifaceted investigations in 200 subfertile men. The results of the chromosome studies have been correlated retrospectively with clinical, seminal and endocrinological features, with histological findings in testicular biopsies and with the response to treatment.

Patients and Investigations

This study includes 204 subfertile men (at least 1 sperm count less than 20 million per ml or motility consistently less than 30% at 3 hours) who were investigated and treated at the Male

Table I

Incidence of Abnormalities and Variants in Somatic Chromosomes related to Average Pre-treatment Sperm Counts and Incidence of Pregnancies in the Spouse (198 Cases)

Somatic chromosomes		No. of cases	Average sperm count (m/ml)				Pregnancy
			0	<5	6-20	>20	
Abnormal (7 cases)	47,XXY	3	2	1	...	...	...
	46,XY/47,XXY	1	1	...	...	...	...
	46,XY t(D/D)**	1	...	...	1	...	...
	46,XY t(D/E)	1	1	...	...	...	...
	46,XY t(Y/F)	1	1	...	...	...	...
Variant (21 cases)	46,XYq+/−	15	2	6	7	...	3 (20%)
	Other Y variants	6	4	...	1	1	...
Normal	46,XY	170*	43	37	55	34	23 (13·5%)

* 1 patient refused seminal analysis.
** t = translocations.

Table II

Incidence of Meiotic Abnormalities related to Treatment Groups and Average Pre-treatment Sperm Counts (204 Cases)

			Meiotic chromosomes					
Treatment group	Average sperm count (m/ml)	Number of cases	Normal (68 cases)	?normal ?abnormal (47 cases)	Abnormal (41 cases)*	No meiosis (24 cases)	Not classified (20 cases)	Not done (4 cases)
Varicocele (68 cases)*	<5	18	7 (39%)	5	4 (22%)	...	2	...
	6-20+	49	17 (35%)	14	9 (18%)	...	8	1
Oligozoospermia (81 cases)	<5	27	4 (15%)	8	6 (22%)	5	4	...
	6-20	43	20 (47%)	7	12 (28%)	1	2	1
	>20	11	5 (45%)	2	3 (27%)	...	1	...
Azoospermia (55 cases)	0	55	15 (27%)	11	6 (11%)	18 (33%)	3	2

* 1 refused seminal analysis.

Table III

Relationship between Abnormalities and Variants in Somatic Chromosomes and Abnormalities in Meiosis (198 Cases)

		Meiotic chromosomes					
Somatic chromosomes	No. of cases	Normal	?normal ?abnormal	Abnormal	No meiosis	Not classified	Not done
47,XXY	3	...	1	...	2	...	...
46,XY/47,XXY	1	...	...	...	1	...	...
Somatic translocations	3	...	...	3	...	...	...
46,XYq+/−	15	3 (20%)	2	4 (27%)	2	2	2
Other Y variants	6	2	2	1	1	...	...
Normal	170	62 (36·5%)	41	32 (19%)	18	15	2

Fertility Clinic at the Chelsea Hospital for Women by methods which have been described previously (Hendry *et al.*, 1973). Basic investigations included clinical examination, seminal analysis judged on at least 2 specimens produced after 2 to 4 days abstinence and measurement of plasma testosterone (PT) and 24-hour urinary excretion of luteinising hormone (LH) and follicle stimulating hormone (FSH) by radioimmunoassay (Collins *et al.*, 1972). All patients in this study had small testicular biopsies taken under general anaesthesia.

Tissue for histological examination was fixed in Bouin's solution and stained with haematoxylin and eosin. Spermatogenesis was assessed by one observer (R. C. B. P.) according to the method described by Johnsen (1970). This provides a testicular biopsy score count, which is expressed as a figure between 1 (no cells in tubular section) and 10 (normal complete spermatogenesis).

Somatic chromosomes were studied in peripheral blood lymphocytes (198 patients). In the early part of the study only conventional staining was used; more recently G- and C-banding techniques have also been applied for the purpose of precise chromosome identification. Meiosis was studied in testicular tissue (200 cases) by the air-drying technique described by Meredith (1969). This technique was adopted because it has been our experience that cell suspension air-drying methods, although giving more elegant preparations, tend to result in loss of cells, which can be a serious drawback when material is limited and cells are few, as they often can be in infertile males. The tubules were fixed and then impressions were made and very lightly stained with orcein for 3 min. Meiosis was judged by one observer (P. E. P.) as normal, ?normal/?abnormal, abnormal or no meiosis. 10% were not classified due to unsatisfactory preparations.

The chromosome, histological and endocrine studies were carried out independently and without reference to each other but treatment was applied in the light of the findings which were transmitted to one of us (W. F. H.). The one exception was the results of the meiotic studies, which only exceptionally were made known during treatment—namely, when a potentially dangerous abnormality was found. These patients were given genetic counselling at the Paediatric Research Unit at Guy's Hospital.

Treatment

68 patients with oligozoospermia had varicoceles which were ligated by the technique previously described (Hendry *et al*, 1973). 18 of these patients subsequently received additional treatment with mesterolone 100 mg daily for up to 1 year and a further 9 received fluoxymesterone 5 mg daily for up to 6 months.

81 patients with oligozoospermia had no varicocele. These patients were treated with mesterolone 100 mg daily for up to 1 year. 15 subsequently received fluoxymesterone 5 mg daily for up to 6 months.

55 cases had azoospermia. 18 patients with good-size testes underwent epididymo-vasostomy; 8 had varicoceles which were ligated. 4 patients had bilateral absence of vasa and 1 had bilateral obstruction of vasa after treatment of bladder exstrophy. 24 patients were recommended for AID or adoption once the histological result of the testicular biopsy was known.

Response to treatment was rated as *good* if the sperm count rose to levels of consistently more than 20 m/ml with at least 30% moving actively within 3 hours of production. The response was considered *fair* if distinct improvement occurred but failed to exceed these levels, or was inconsistent. If the sperm count stayed the same or deteriorated the response was rated as *poor.*

Results

Somatic Chromosomes

The results of the somatic chromosome studies are shown in Table I, related to the average pre-treatment sperm counts and incidence of pregnancies in the spouse.

7 patients (3·5%) showed definite somatic chromosome abnormalities. 3 had Klinefelter's syndrome of the 47,XXY type and 1 had 46,XY/47,XXY mosaicism. These patients had azoospermia or severe oligozoospermia. 3 patients had translocations detected in all somatic cells. These are recorded in Table I. 2 had azoospermia but the 3rd had sperm counts of around 10 million per ml.

21 cases (10·5%) showed variants of the Y chromosome. 13 were 46,XYq+ and 2 were 46,XYq−; these patients had similar sperm counts to those with normal somatic chromosomes and 3 (20%) achieved pregnancies. 6 patients had other variants of the Y chromosome: 4 of these were azoospermic. Other somatic chromosome variants are still being studied by the special banding techniques.

Excluding variants somatic chromosomes were normal in 170 cases (86%). 23 of these patients (13·5%) achieved pregnancies.

Table IV

Normal Meiosis: Histological and Endocrine Results (Mean ± S.D.) related to Average Pre-treatment Sperm Counts (68 Cases)

Average sperm count (m/ml)	No. of cases	Histology (mean Johnsen score ± S.D.)	Hormone levels (mean ± S.D)		
				Urinary (I.U./24 hr)	
			PT (nG/100 ml)	LH	FSH
0	15	8·38 ± 2·4	372 ± 168	24 ± 9	15 ± 8
< 5	11	7·8 ± 1·8	274 ± 190	25 ± 10	37 ± 28
6-20	27	8·6 ± 0·7	411 ± 166	24 ± 16	14 ± 6
> 20	15	9·3 ± 0·3	380 ± 146	21 ± 8	17 ± 9

Table V

Abnormal Meiosis: Histological and Endocrine Results (Mean ± S.D.) related to Average Pre-treatment Sperm Counts (40 Cases*)

Average sperm count (m/ml)	No. of cases	Histology (mean Johnsen score ± S.D.)	Hormone levels (mean ± S.D.)		
				Urinary (I.U./24 hr)	
			PT (nG/100 ml)	LH	FSH
0	6	5·7 ± 3·2	415 ± 168	28 ± 6	29 ± 27
< 5	10	7·5 ± 1·6	344 ± 218	37 ± 26	27 ± 19
6-20	17	8·5 ± 1·2	457 ± 160	25 ± 9	17 ± 9
> 20	7	8·6 ± 0·7	391 ± 210	18 ± 6	13 ± 7

* 1 patient refused seminal analysis.

Meiotic Chromosomes

Meiosis was normal in 68 cases, ?normal/?abnormal in 47 and abnormal in 41. No meiosis was found in 24 cases, which theoretically could reflect one of 3 situations: inadequate biopsy material, inadequate chromosome preparations, or a true meiotic abnormality with absent or seriously impaired spermatogenesis. In 20 patients it was not possible to reach a conclusion as to meiosis and these were not classified. The distribution of these findings by treatment groups and sperm counts is shown in Table II. It is clear that abnormalities occur with a similar frequency in each of these groups, although relatively few patients with severe oligozoospermia without varicoceles had demonstrably normal meiosis. Many patients (33%) with azoospermia had no meiosis.

The relationship between abnormalities and variants in somatic chromosomes and abnormalities in meiosis is shown in Table III. As might be expected, all patients with definite somatic chromosome abnormalities showed meiotic abnormalities as well. However, there seemed to be only a very slight increase in meiotic abnormalities in patients with Y-variants.

Histological and endocrine results for those patients with definitely normal meiosis are shown in Table IV and may be compared with those of patients with definitely abnormal meiosis in Table V. There are few striking differences between these patients, except for the higher Johnsen score count and lower FSH levels in patients with azoospermia and normal meiosis, which reflects

Table VI

No Meiosis: Seminal, Histological and Endocrine Results (Mean ± S.D.) expressed for the Whole Group (24 Cases)

Average sperm count (m/ml)	No. of cases	Histology (mean Johnsen score ± S.D.)	Hormone levels (mean ± S.D.		
				Urinary (I.U./24 hr)	
			P.T. nG/100 ml	LH	FSH
*0	18	2·1 ± 0·7	325 ± 147	40 ± 22	59 ± 30
<5	5				
6-10	1				

* None responded to treatment.

Table VII

Normal Meiosis: Response to Treatment and Incidence of Pregnancies in the Spouse, related to Average Pre-treatment Sperm Counts (68 Cases)

Average sperm count (m/ml)	No. of cases	Response to treatment			
		Poor	Fair	Good	Pregnancy
0	15	15	...	...	...
<5	11	10	1	...	...
6-20	27	3	10	14	8
>20	15	2	4	9	4

the high incidence of obstruction in this group. In patients with no meiosis (Table VI) the mean Johnsen score count was very low and FSH levels were very high.

Response to treatment and incidence of pregnancies in the spouse in patients with normal and abnormal meiosis are shown in Tables VII and VIII. For patients with moderate oligozoospermia, good response to treatment and pregnancies in the spouse were much more common in the presence of normal meiosis. Nevertheless 5 pregnancies were produced by patients with abnormal meiosis, all of whom showed evidence of gonadal mosaicism. All patients with no meiosis showed a poor response to treatment.

The meiotic abnormalities observed are summarised in Table IX and will be described in detail elsewhere. Normal meiotic chromosome preparations are shown in Figure 1 (a-f). These may be compared with examples of observed abnormalities which are illustrated in Figure 2 (a-f).

Supernumerary chromosomes were observed in 13 cases at meiosis (Fig. 2, a and b). Although many of these patients showed a poor response to treatment, 3 pregnancies were produced by these patients.

In 4 cases, the pachytene formation resembled that usually seen in females (Fig. 2c). This finding was associated with severe oligozoospermia and poor response to treatment in 3 of 4 cases.

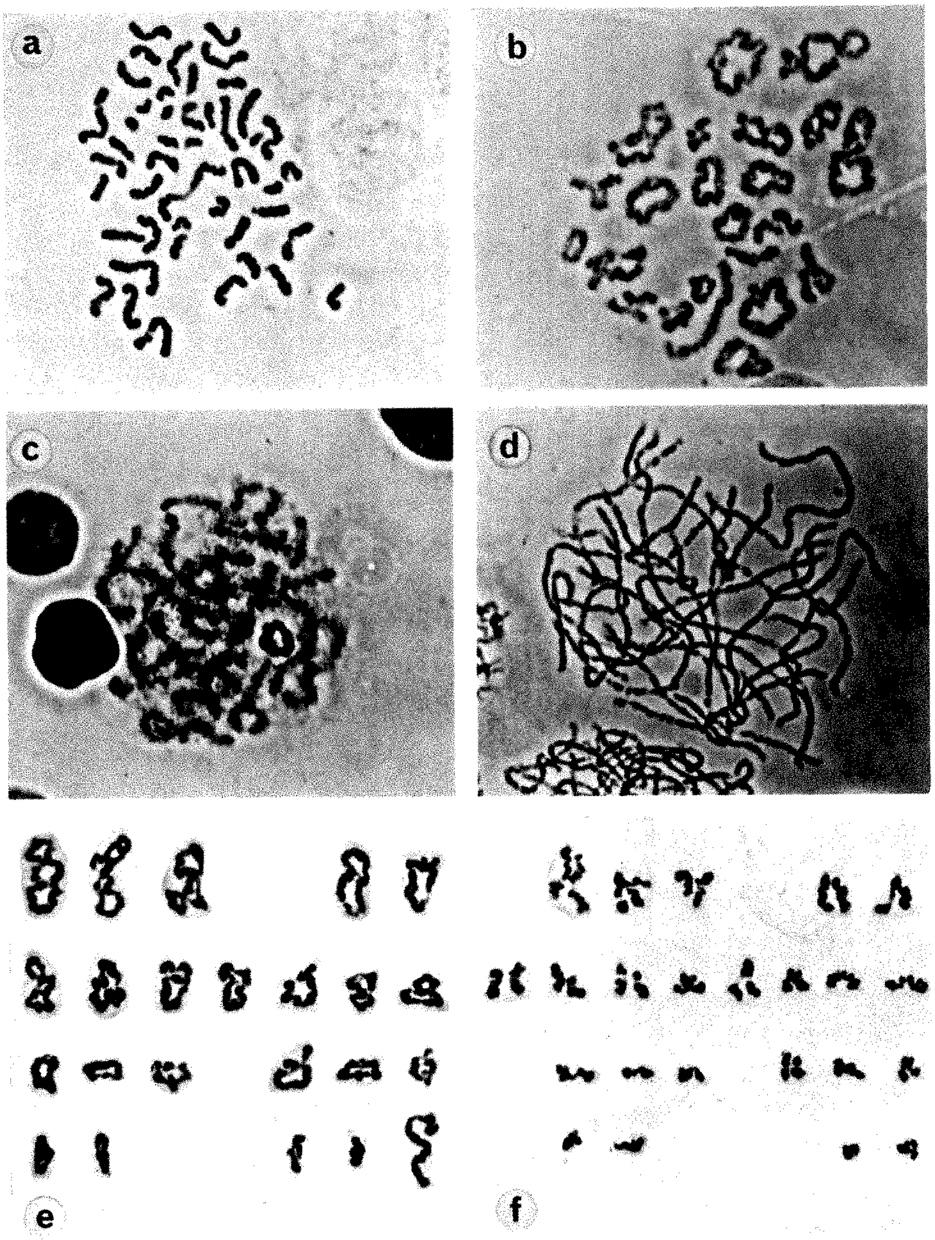

Fig. 1. (Enlargement approximately ×2,000.) (a) Normal spermatogonial metaphase with 46 chromosomes (23 pairs). The thinning corresponding to some centromeres and the close apposition of the chromatids that make up each chromosome, should be noted. (b) Normal first meiotic metaphase which shows the paired chromosomes that form 23 bivalents, each made up of 2 chromosomes (see e). These are associated side by side with the exception of the sex bivalent in which the X and Y chromosomes are terminally associated (at 6 o'clock). The chiasmata which correspond to crossing-over points tie together the chromosomes of the individual autosomal bivalents. (c) Pachytene chromosome threads of normal male meiotic prophase. Note the feathery appearance of the closely apposed paired chromosomes. The sex bivalent ("sex vesicle") forms a distinct, densely staining body at 3 o'clock. (d) Pachytene configurations of the normal female seen during the meiotic prophase which takes place *in utero*. Note the different appearance from (c). (e) Bivalents of a normal first meiotic metaphase displayed as a karyotype. The first autosomal bivalent has 4 chiasmata. The second has 5 chiasmata and 1 twist between the paired chromosomes. The terminal association between the sex chromosomes is not scored as a chiasma. The total chiasmata for this cell is 56. (f) 23 individual chromosomes of the haploid normal second meiotic metaphase arranged as a karyotype. It contains the X chromosome. Each chromosome consists of 2 chromatids which, as in a somatic mitosis, will separate from each other at cell division.

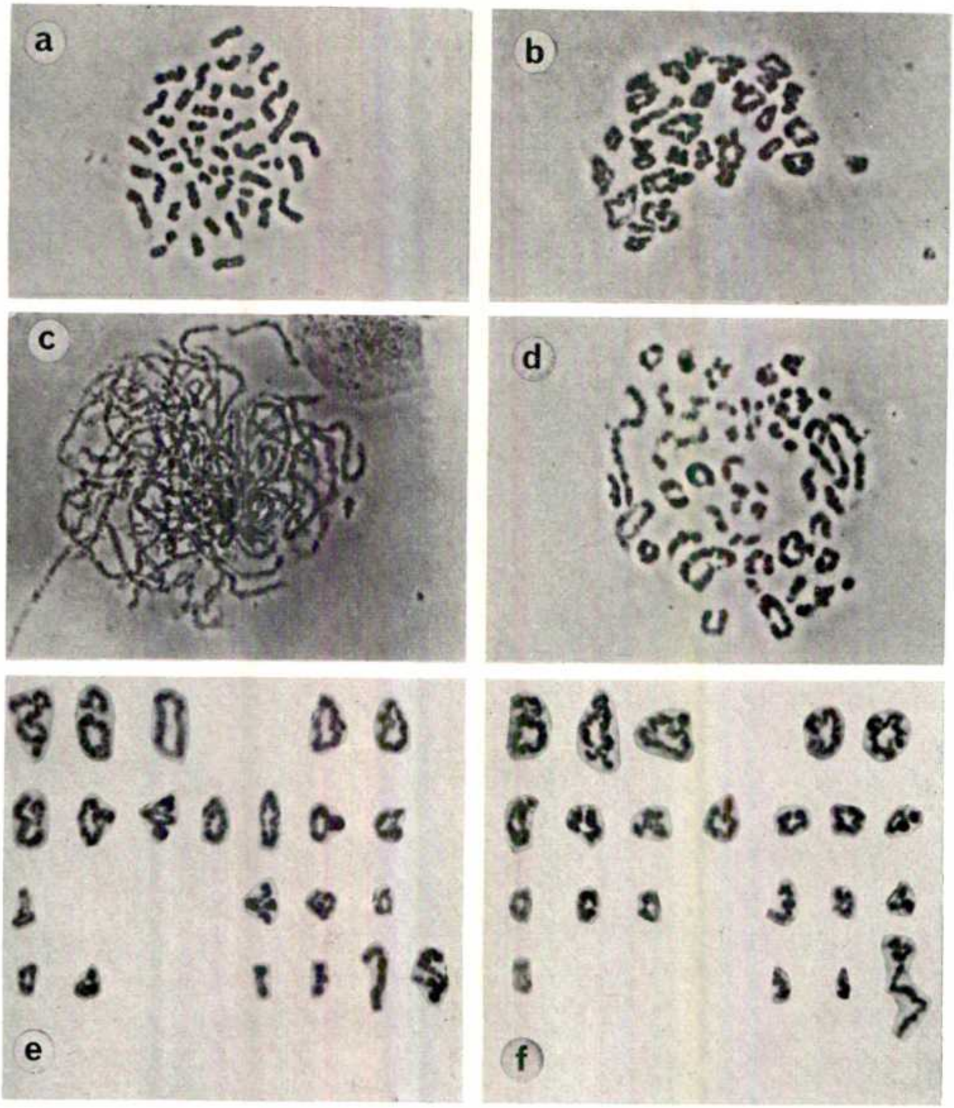

Fig. 2. (Enlargement approximately × 2,000.) (a) Abnormal spermatogonial metaphase with 47 chromosomes owing to the presence of a supernumerary element of unknown make-up. (b) Abnormal first meiotic metaphase with 24 bodies. One of these—probably the one at 3 o'clock—is a supernumerary element of unknown constitution. Morphologically it may be an extra bivalent or, possibly, a univalent. (c) Abnormal female-type pachynema. (d) Abnormal first meiotic metaphase with a gross reduction of the total number of chiasmata. (e) Abnormal first meiotic metaphase arranged as a karyotype from a male with a D/D translocation. It contains 22 bodies, one of which is a trivalent (bottom row, extreme right). This consists of the D/D chromosome, each arm of which is made up of a specific D-group chromosome and therefore pairs with the partner chromosomes of the D-group. (f) Abnormal first meiotic metaphase displayed as a karyotype with 22 bodies. The sex element (bottom right) is abnormal because the Y chromosome is involved in a translocation with an autosome of the F-group. When the chromosomes pair during the meiotic prophase this leads to the formation of a chromosome chain made up as follows: the X chromosome which associates as usual with the Y chromosome and this carries the translocated F chromosome. It is this latter which, in turn, pairs with the free partner F chromosome which is homologous to the one translocated on to the Y chromosome.

Table VIII

Abnormal Meiosis: Response to Treatment and Incidence of Pregnancies in the Spouse, related to Average Pretreatment Sperm Counts (40 Cases*)

Sperm count (m/ml)	No. of cases	Response to treatment			
		Poor	Fair	Good	Pregnancy
0	6	6	...	...	...
<5	10	9	1	...	1†
6-20	17	7	8	2	4†
>20	7	2	1	4	...

* 1 patient refused seminal analysis. † Mosaics

Table IX

Meiotic Abnormalities observed, and Incidence of Mosaicism, related to Histology (Mean ± S.D. Johnsen Score Count), Response to Treatment and Incidence of Pregnancies in the Spouse

Meiotic Abnormality	Number of cases	Number of Mosaics	Histology (mean Johnsen count ± S.D.)	Response to treatment			Pregnancy
				Poor	Fair	Good	
Supernumerary* chromosomes	13	10	8·0 ± 1·4	6	6	...	3†
"Female" pachytenes	4	...	7·6	3	...	1	...
Low chiasma frequency and asynapsis	11	1	8·0 ± 1·6	6	2	3	...
Translocations	8	4	8·3 ± 1·4	5	1	2	1†
Meiotic arrest	3	...	6·8 ± 3·0	2	1	...	1
Miscellaneous	2	...	8·6 ± 0·1	2	...	...	...

* 1 patient refused seminal analysis. † Pregnancies occurred with observed mosaicism.

Low chiasma frequency and asynapsis, or desynapsis, was seen in 11 cases (Fig. 2d): response to treatment was poor in most of these cases and although 3 showed a remarkable increase in sperm count with treatment (one sperm count rose to 1,300 m/ml), no pregnancies were obtained.

Translocations were observed in 8 cases (Fig. 2e and f). In 3 of these cases, somatic translocations had also been observed. In 4 of the other 5 patients, response to treatment was poor, 1 patient, who was found to be a gonadal mosaic for a translocation, fathered a perfectly normal child.

Meiotic arrest was difficult to interpret solely on the grounds of chromosome studies of meiosis but appeared to correlate with a low average Johnsen Score Count. 1 patient in this group produced a pregnancy.

Finally, 1 patient showed a possible anaphase block which might possibly be the result of meiotic mutation and 1 showed a hypoploid cell line. Both responded poorly to treatment.

Discussion

Definite abnormalities in meiotic chromosomes have been defined in 20% of the 200 subfertile men in this study, although somatic abnormalities were found in only 3·5%. Supernumerary chromosomes, translocations and low chiasma frequency and asynapsis are well recognised in association with male infertility (Kjessler, 1966; Hultén, Eliasson and Tillinger, 1970; Dutrillaux and Guéguen, 1971; Laurent *et al.*, 1973; Skakkebaek, Bryant and Philip, 1973). We also found unusual pachynemas with poor meiotic figures at first meiotic division (MI) and interpret these as morphologic evidence of abnormalities in the meiotic process. We have called these "female-type" pachynemas as they resemble those of the human female observed during intrauterine development. The high incidence of mosaicism—using this word in a strict observational sense—suggests that at least some of these abnormalities may have occurred as mutations within the germinal line which seriously impair the spermatogenic process.

Meiotic arrests are best defined by histological techniques and are difficult to interpret cytogenetically. Many of these cases have been included in the ?normal/?abnormal group. These cases have not been considered in this communication but will be the object of further detailed study. Again, one feels that some of these cases could reflect meiotic mutations with subsequent impairment of gametogenesis.

The absence of meiosis on cytogenetic study correlated well with the histological findings and its association with elevated urinary FSH levels indicated failure of spermatogenesis in these patients.

These studies indicate that chromosome abnormalities detected in meiosis may account for impairment of spermatogenesis in at least 20% of subfertile men. In a few more the presence of aberrations was suspected but could not be accurately defined. Most of the patients with definite abnormalities responded poorly to treatment, compared to those who were demonstrably normal. However, most of the abnormalities occurred as mosaics and a few normal pregnancies were produced by patients with meiotic abnormalities. Therefore, these abnormalities do not necessarily constitute a contra-indication to treatment, as some normal pregnancies can still be produced. Potentially dangerous abnormalities such as translocation are rare, and are usually associated with severe impairment of fertility. However, if these are detected it is essential to offer genetic counselling to these few patients. Any pregnancy which is produced could be checked at an early stage by amniocentesis for prenatal diagnosis of abnormality.

Summary

Somatic and meiotic chromosomes have been studied prospectively in 200 subfertile males. The results have been correlated with clinical, seminal and endocrinological features, with histological findings in testicular biopsies and with response to conventional treatment.

Somatic chromosome abnormalities were found in 3·5% of cases and variants of the Y chromosome were found in 10·5%. Definite abnormalities in meiotic chromosomes were observed in 20% of these patients, including supernumerary chromosomes, low chiasma frequency and asynapsis, and translocations. Many of these abnormalities occurred as mosaics, presumably a result of meiotic mutation. In 4 cases, a previously unrecognised abnormality in pachynemas has been defined. Absence of meiosis was found in 12% of cases, which correlated well with the histological findings of germinal cell aplasia and elevated urinary FSH levels.

It is concluded from this preliminary analysis that abnormalities in meiosis may account for the decreased spermatogenesis and poor response to treatment in at least 20% of subfertile men. However, these abnormalities do not constitute a contra-indication to treatment as normal pregnancies can still be produced, in a few cases albeit, sometimes requiring monitoring.

We wish to thank the Departments of Illustration and Medical Photography at the Institute of Urology for their help with the tabulations, and Miss Anthea Minchom who prepared the typescript.

Mr L. Dixon and Mrs J. Kelberman are warmly thanked for meiotic work, Mr J. Crolla for the chromosome banding, and Mr L. Kelberman for the photography. Financial support from the D.H.S.S., the Spastics Society and an anonymous donor is gratefully acknowledged.

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The Actions of Prostaglandins on the smooth muscle of the Human Urinary Tract *in vitro*

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"Just as the steroid hormones were the dominant clinical development of the 1960s, the 1970s may well be the era of prostaglandins" (Karim, 1971).

In 1930 details of an experiment were published in which fresh human seminal fluid was found to cause uterine muscle contraction (Kurzrok and Lieb, 1930). The substances responsible were identified as lipid soluble fatty acids and in 1935 von Euler termed them "prostaglandins" (Euler, 1935). This term proved a misnomer as the seminal vesicles are the chief source of seminal fluid prostaglandin. Since their discovery, 40 years ago, prostaglandins have been the subject of much scientific and clinical research.

Prostaglandins can be isolated from many mammalian tissues and have effects on most body systems. In the gastro-intestinal tract they increase motility, may be responsible for the maintenance of gut muscle tone and because of their action of inhibition of gastric acid secretion have been considered as therapeutic agents in the treatment of peptic ulceration (Wilson, Phillips and Levine, 1970). Prostaglandins may also prove useful in the treatment of asthma as prostaglandin E_1 has been shown to decrease airway resistance by its broncho-dilating effect (Cuthbert, 1969). Prostaglandins have important effects on blood vessels; they may be vasoconstrictors or vasodilators and have an essential role in the pathogenesis of inflammation. However, it is in the field of obstetrics that prostaglandins find their best known clinical application. Their ability to initiate and maintain uterine contractions is used to induce labour or abortion.

Despite numerous reports on the properties of prostaglandins, many with reference to their action on smooth muscle, no papers have been published on their actions on the smooth muscle of the human urinary tract. Seminal fluid is the richest source of prostaglandins in the animal kingdom, containing 13 of the 14 naturally occurring prostaglandins. These prostaglandins are measurable in milligram quantities (Hamberg and Samuelsson, 1966). Considering the high concentrations of prostaglandins ejaculated into the prostatic urethra and into the vaginal vault, where absorption can take place, a study of the actions of prostaglandins on human urinary tract musculature seemed appropriate, if not overdue (Karim and Sharma, 1971).

Materials and Methods

14 experiments were performed, 10 on specimens of bladder muscle and 4 on ureteric muscle samples. In 10 patients bladder muscle was removed in a strip, approximately 4 cm × 0·5 cm, at open cystotomy. The ureteric muscle samples were taken from surgical specimens removed from 4 patients. The specimens were transported in Hartmann's solution cooled to 5°C. The specimen was then dissected into thinner strips 2 cm × 0·25 cm and set up in a superfusion apparatus (Gaddum, 1953).

Muscle contractions were recorded isotonically using a liquid potentiometer (Rogers, 1967). The muscle strip was suspended from the potentiometer lever in a continuous flow of Krebs' solution (5 ml/min). The Krebs' solution was saturated with 95% oxygen and 5% carbon dioxide and warmed to 37°C (Fig. 1). The specimen had to be thin to allow diffusion of essential nutrients

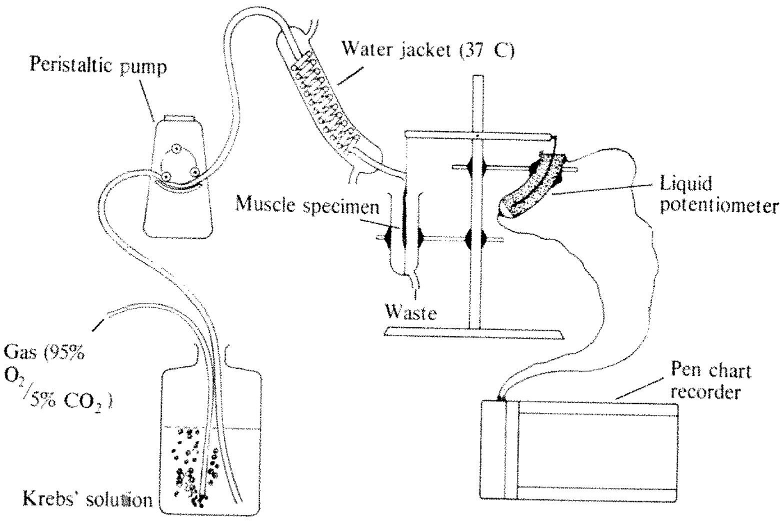

Fig. 1. Superfusion apparatus.

to all the muscle fibres. An injection point was provided to allow the introduction of the test substances into the flow of Krebs' solution. The muscle contractions resulted in a change of electrical charge produced by the potentiometer. These changes were recorded on a pen chart recorder.

In each experiment the effects of adding acetylcholine, adrenalin and the four prostaglandins, PGE_1, PGE_2, $PGF_{1\alpha}$ and $PGF_{2\alpha}$ were recorded. These 4 prostaglandins may be considered derivatives of prostanoic acid.

In 3 bladder experiments the effect of adding methysergide, mepyramine maleate, atropine, phenoxybenzamine and propranolol was assessed. These compounds are antagonists to 5-hydroxytryptamine, histamine, acetylcholine, adrenalin and noradrenalin, all of which may act as neurotransmitting agents.

Results

Each experiment was allowed to stabilise for 2 hours.

(a) Bladder Muscle (10 Experiments)

After the stabilisation period all specimens showed spontaneous rhythmic contractions (Fig. 2). These contractions occurred with a frequency of between 5 and 8 per min.

1. *Acetylcholine*

In all cases acetylcholine administration resulted in bladder muscle contraction (Fig. 2). The minimum dose producing a contraction was 10 nannograms (10×10^{-9} grams) and a maximal response was obtained with 5 micrograms (5×10^{-6} grams) of acetylcholine.

2. *Adrenalin*

In each case adrenalin in a concentration of 5 micrograms (μg) led to a relaxation of the bladder muscle strips (Fig. 3).

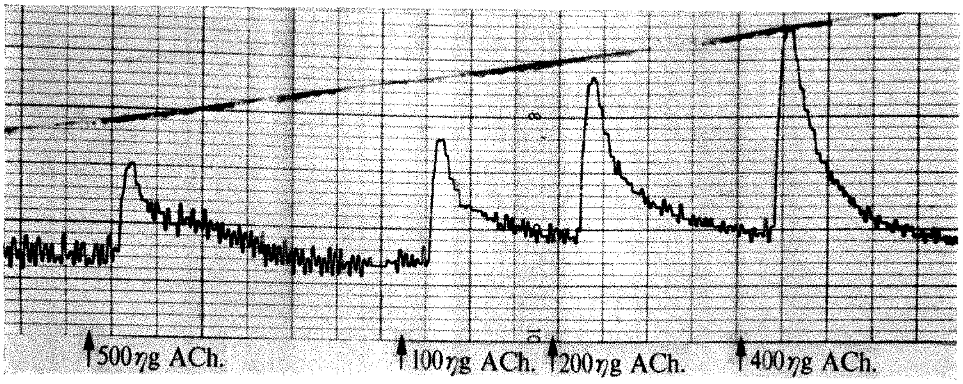

Fig. 2. Basic rhythmic activity and the actions of increasing concentrations of acetylcholine on human bladder muscle.

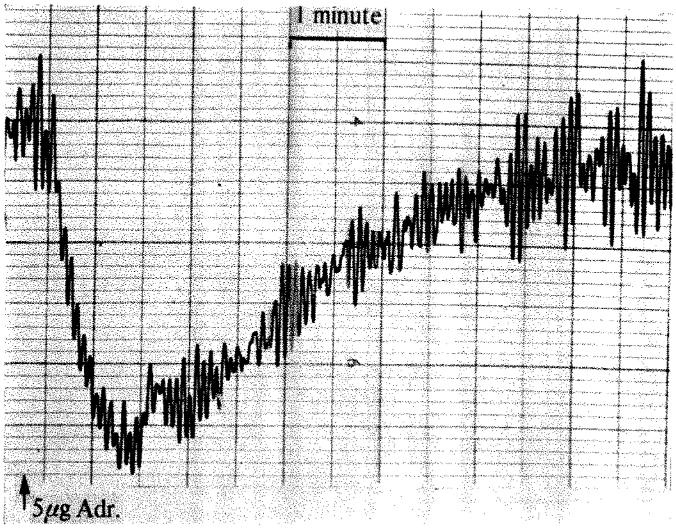

Fig. 3. Response of bladder muscle to adrenalin.

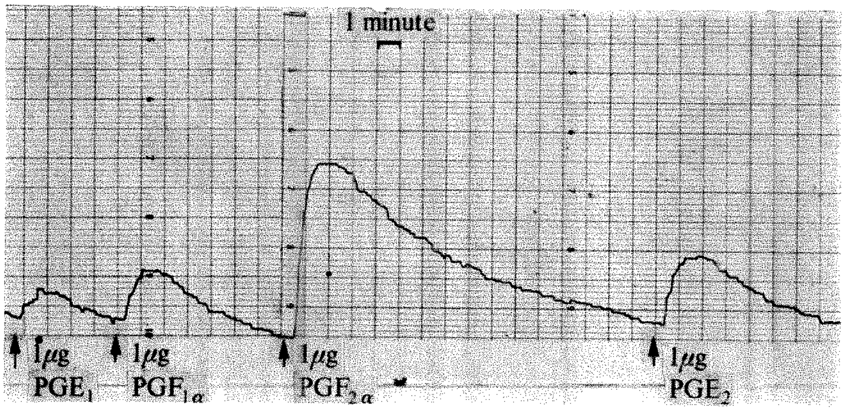

Fig. 4. Response of bladder muscle to the 4 tested prostaglandins.

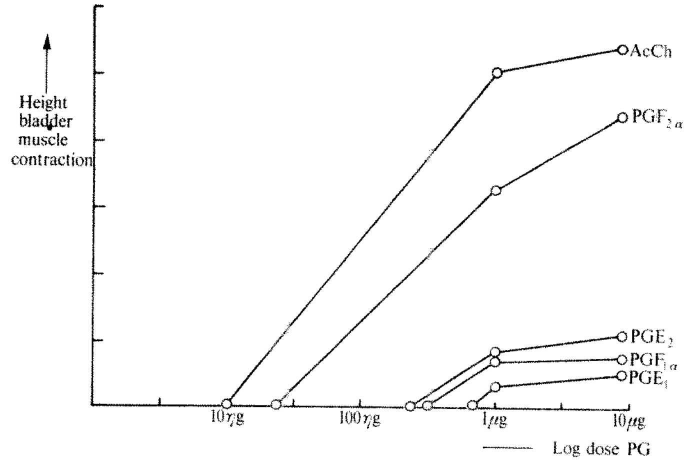

Fig. 5. Dose-response curves for acetylcholine and the 4 tested prostaglandins (mean values from 10 bladder muscle experiments).

3. *Prostaglandins*

In every case each prostaglandin caused the bladder muscle strip to contract (Fig. 4). In all 10 experiments PGE$_1$ was the least active and PGF$_{2\alpha}$ the most potent. PGE$_2$ and PGF$_{1\alpha}$ had equal contractile activity being less potent than PGF$_{2\alpha}$ but having more than twice the activity of PGE$_1$. The minimum concentrations of prostaglandins needed to stimulate muscle contraction were PGF$_{2\alpha}$ 20 nannograms (ng), PGF$_{1\alpha}$ and PGE$_2$ 150 ng and PGE$_1$ 500 ng. Each dose response curve was linear until a concentration of between 1 μg and 3 μg. A maximal response was quickly obtained with concentrations of between 3 μg and 8 μg. The relative potencies of the prostaglandins may be compared with the activity of acetylcholine. Using the data from 10 bladder experiments the mean contraction heights were calculated and dose response curves were drawn (Fig. 5). The contractile activity of PGF$_2$ approaches that of acetylcholine. The 3 other prostaglandins showed much less activity. The activities of the prostaglandins were also related to that of acetylcholine by assuming the contractile activity of acetylcholine to be 100%. The mean contraction heights obtained with a concentration of 1 μg was calculated. The activities of the prostaglandins were PGF$_{2\alpha}$ 64·8%, PGE$_2$ 15·4%, PGF$_{1\alpha}$ 13·9% and PGE$_1$ 6·1%.

Acetylcholine and the prostaglandins stimulated the bladder muscle strips to contract. However, the type of contraction differed (Fig. 2 and 6). Acetylcholine produced a fast contraction followed by a rapid relaxation whereas the prostaglandins induced a slower contraction with a relaxation phase lasting up to 20 min.

In the 3 experiments in which a mixture of neurotransmitter antagonists was added to the Krebs' solution no change in the prostaglandin activity was observed.

(b) Ureteric Muscle (4 Experiments)

After the stabilisation period each specimen showed spontaneous contractions of a frequency of 1 to 3 per min.

1. *Acetylcholine*

The administration of acetylcholine led to an inhibition of ureteric muscle contraction at a concentration of 2 μg in 3 of the experiments (Fig. 7). In the other experiment a similar contraction resulted in unaltered contractions.

2. *Adrenalin*

In each experiment adrenalin in a concentration of 2 μg resulted in more frequent contractions (Fig. 7).

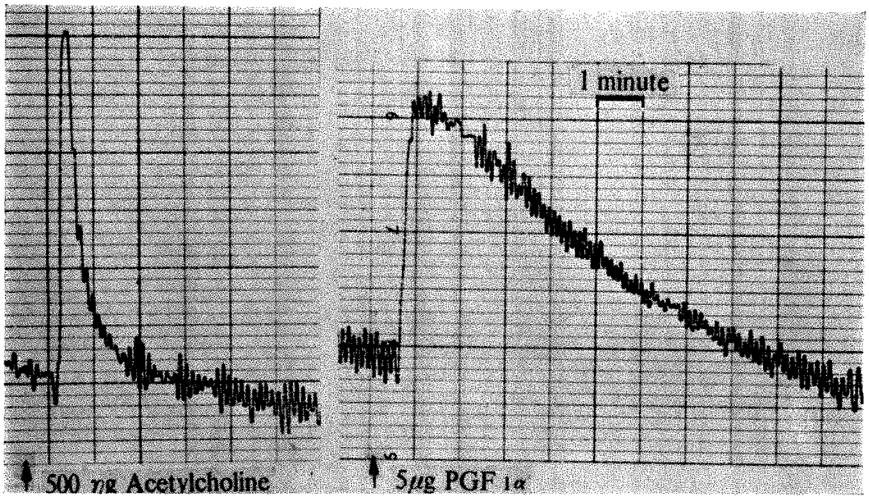

Fig. 6. Comparisons of the type of contraction produced in the same bladder muscle experiment by acetylcholine and prostaglandin $F_{1\alpha}$.

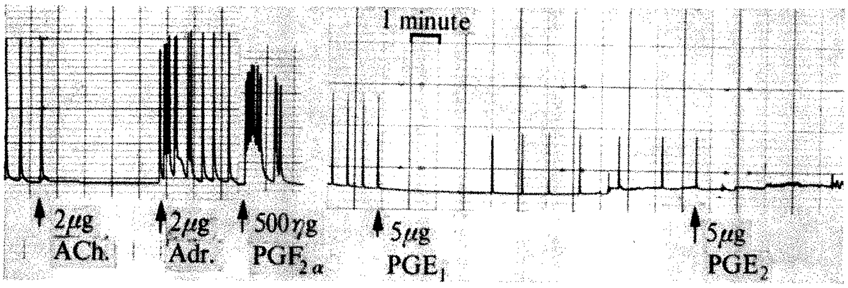

Fig. 7. Response of 2 specimens of ureteric muscle to acetycholine, adrenalin, $PGF_{2\alpha}$, PGE_2 and PGE_1.

3. *Prostaglandins*

The results lacked consistency but in general F series prostaglandins led to increased ureteric muscle contractions whereas the E series prostaglandins caused the inhibition of contractions (Fig. 7).

A summary of the actions of acetylcholine adrenalin and the prostaglandins PGE_1, PGE_2. $PGF_{1\alpha}$ and $PGF_{2\alpha}$ is presented (Table).

Discussion

Most of the recent interest in urinary tract pharmacology has centred on the demonstration of cholinergic and adrenergic activity and their neuronal receptors. We have used the well established actions of acetylcholine and adrenalin on urinary smooth muscle as the basis for our study on prostaglandins (Todd and Mack, 1969). A constant pattern of response was obtained for all 10 bladder experiments and to a lesser extent for the 4 ureteric samples. The results of this study are in accord with those published on animal work (Boyarsky, Labay and Gerber, 1966; Struthers, 1973; Taira, 1974).

Table

Summary of Effects of Tested Substances on Human Smooth Muscle *in vitro*

		Bladder	Ureteric
Acetylcholine		Contraction	Relaxation
Adrenalin		Relaxation	Contraction
Prostaglandins	E	Contraction	Relaxation
	F	Contraction	Contraction

The mode of action of prostaglandins is unknown but believed to be direct rather than through a neurotransmitter such as acetylcholine, histamine or 5-hydroxytryptamine (Taira, 1974). The present study would support this view. When antagonists to these neurotransmitters were added to the Krebs' solution the actions of prostaglandin remained unchanged.

Acetylcholine has been shown to cause a different type of contraction than that due to prostaglandins. The fast contraction of short duration induced by acetylcholine is in keeping with its function as the neurotransmitter in the act of voiding (Fig. 6). The long, slow contraction after prostaglandin administration suggests a different mechanism and a different function. Prostaglandin-like substances have been found in vesical vein samples taken from dogs undergoing bladder distension. The suggestion has been made that prostaglandins allow the bladder to accommodate to or to resist filling (Gilmore and Vane, 1971). A similar function has been proposed for prostaglandins in the stomach (Piper and Vane, 1971). However lower down in the gastrointestinal tract prostaglandins are largely stimulatory to gut muscle (Bennett and Fleshler, 1970).

From the present study the role of prostaglandins in ureteric function is not clear. However the results of the 10 bladder experiments suggest that prostaglandins may be responsible for the maintenance of bladder muscle tone. Further investigation is necessary to establish whether abnormalities of prostaglandin metabolism are associated with lower urinary tract disorders.

Summary

14 experiments, 10 on bladder muscle strips and 4 on samples of ureteric muscle, were performed to examine the actions of 4 prostaglandins (PGE, PGE_2, $PGF_{1\alpha}$ and $PGF_{2\alpha}$) on these tissues. Each of the prostaglandins caused bladder muscle to contract and prostaglandin $F_{2\alpha}$ was the most potent in this respect. The F series prostaglandins also caused increased ureteric muscle contraction whilst those of the E series inhibited contractions. It is likely that contraction is produced by the direct action of prostaglandins on urinary smooth muscle. The suggestion is made that prostaglandins may have a function in the maintenance of vesical tone.

We should like to thank our urological colleagues in the Avon Clinical Area for their active co-operation during this study. The experiments were carried out in the laboratories of the University Department of Physiology in Bristol and we should like to record our appreciation of the assistance given by Dr Allan Rogers and Dr J. A. C. Sykes. Our thanks go to the secretaries in the Department of Urology, Mrs Jean McConnell and Miss Beverley Baker, for their preparation of the manuscript. This work was carried out while the authors were in receipt of an M.R.C. project grant.

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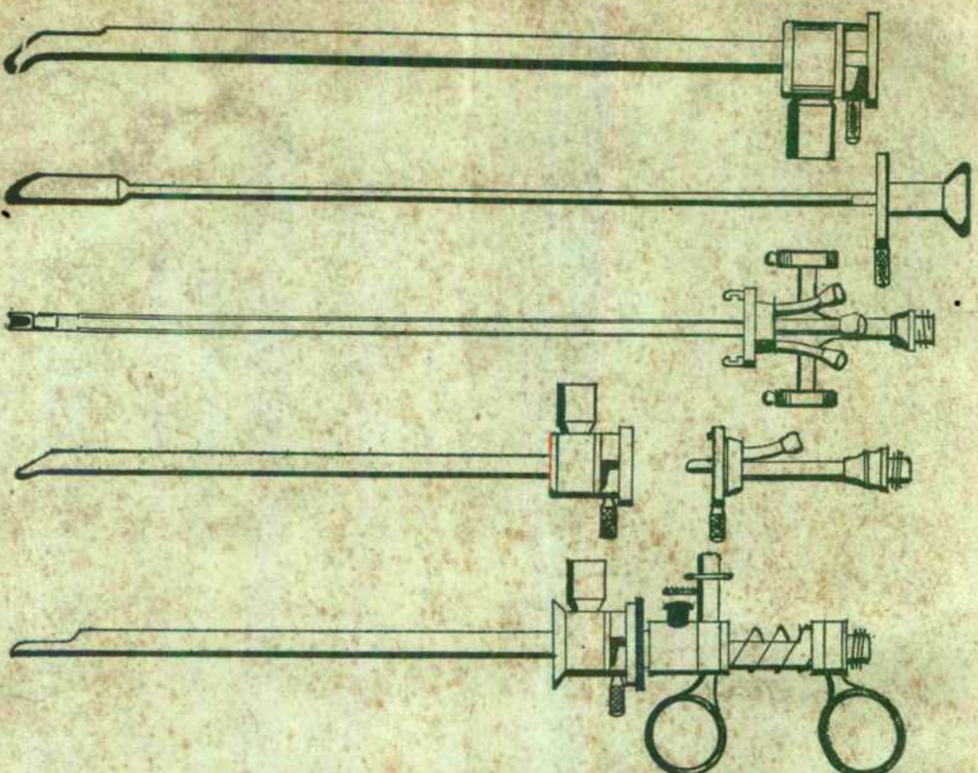

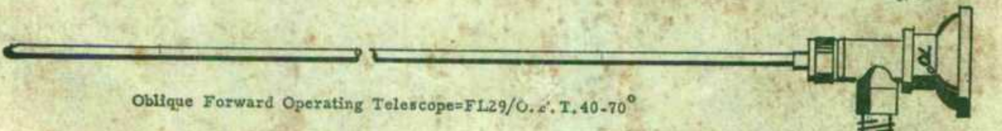

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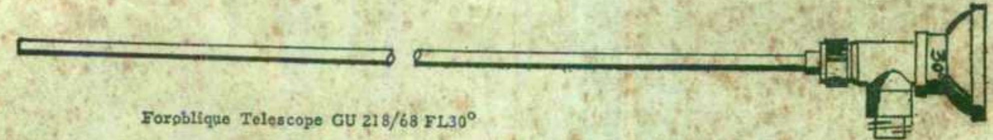

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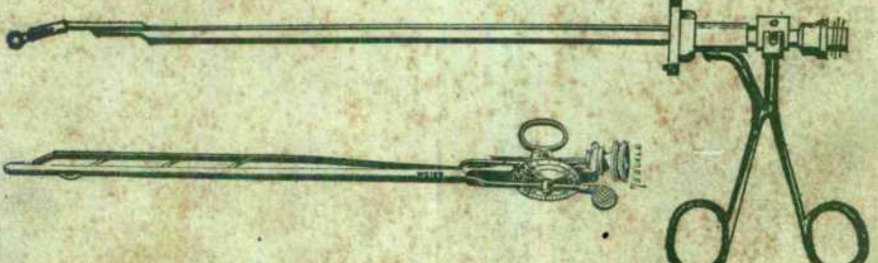

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